22-2153 and 23-1952

United States Court of Appeals for the Federal Circuit

SALIX PHARMACEUTICALS, LTD., SALIX PHARMACEUTICALS, INC., BAUSCH HEALTH IRELAND LTD., ALFASIGMA S.P.A.,

Plaintiffs-Appellants,

– v. –

NORWICH PHARMACEUTICALS INC.,

Defendant-Cross-Appellant.

On Appeal from the United States District Court for the District of Delaware in No. 1:20-cv-00430-RGA, Honorable Richard G. Andrews, Judge

PRINCIPAL AND RESPONSE BRIEF FOR DEFENDANT-CROSS-APPELLANT

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AUGUST 22, 2023

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UNITED STATES COURT OF APPEALS
FOR THE FEDERAL CIRCUIT

CERTIFICATE OF INTEREST

Case Number 22-2153, 23-1952

Short Case Caption Salix Pharmaceuticals, Ltd. v. Norwich Pharmaceuticals, I

Filing Party/Entity Norwich Pharmaceuticals Inc.

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		Alvogen Group, Inc.
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STATEMENT OF RELATED CASES

Norwich has filed suit in the District Court for the District of Columbia seeking an order directing the United States Food and Drug Administration ("FDA") to grant final approval to Norwich's ANDA No. 214369 for rifaximin tablets, 550 mg, for the treatment of irritable bowel syndrome with diarrhea ("IBS-D"). *Norwich Pharmaceuticals, Inc. v. Becerra et al.*, No. 1:23-cv-01611 (D.D.C.)

STATEMENT OF THE ISSUES

Whether the District Court legally erred in implementing the remedy for an act of infringement mandated by 35 U.S.C. § 271(e)(4)(A) in its Final Judgment by declining to reference the hepatic encephalopathy ("HE") indication in Norwich's ANDA – the only basis for the court's infringement finding – and abused its discretion in denying Norwich's motion to modify the Final Judgment under Federal Rule of Civil Procedure 60(b)?

Whether Salix has demonstrated that the District Court committed clear and reversible error in finding that "there was no evidence" that Salix's September 2007 RFIB2001 Press Release disclosed information derived from the work of any inventor(s) and that the District Court therefore erred in finding the RFIB2001 Press Release is prior art under pre-AIA Section 102(a)?

Whether Salix has demonstrated that the District Court committed clear error in finding that the prior art disclosed a dosage range of rifaximin that

encompassed the claimed dosage of 1650 mg per day, or that a POSA would have a reasonable expectation of success in combining the prior art based on evidence of widespread off-label use, success reported in the prior art, and two clinical studies?

Whether Salix has demonstrated that the District Court committed clear error in finding that the prior art disclosed crystalline rifaximin that a POSA would have been motivated to characterize and would have had a reasonable expectation of identifying rifaximin β having the claimed XRPD peaks and water contents?

Whether the District Court erred in finding that Norwich did not prove that claim 4 of the '199 patent is inherently anticipated?

STATEMENT OF THE CASE

I. STATUTORY BACKGROUND

The Federal Food Drug & Cosmetic Act ("FDCA") establishes the requirements for marketing drugs in the United States. In 1984, Congress amended the FDCA (the "Hatch-Waxman Amendments" or "Act") to provide an abbreviated pathway to obtain approval for generic drugs. The Act's central purpose is "'to enable competitors to bring cheaper, generic … drugs to market as quickly as possible.'" *Teva Pharms. USA, Inc. v. Novartis Pharms. Corp.*, 482 F.3d 1330, 1344 (Fed. Cir. 2007) (citing 149 Cong. Rec. S15885 (Nov. 25, 2003)).

Before marketing a new drug, the FDCA requires a drug company to submit a New Drug Application ("NDA") to FDA, and FDA must approve it. *See* 21

U.S.C. § 355(a), (b). The NDA applicant must identify each patent that claims the drug or a method of using the drug. *See* 21 U.S.C. § 355(b)(1)(A)(viii); 21 C.F.R. § 314.53. Once FDA approves an NDA, FDA publishes the patent information submitted by the brand company in a publication known as the "Orange Book." *See* 21 U.S.C. § 355(b)(1)(A)(viii); 21 C.F.R. § 314.53(e).

A company seeking FDA approval for a generic drug must file one of four patent certifications for each Orange Book-listed patent. The relevant certification here is the so-called "Paragraph IV certification," which states that the patent is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the generic drug for which the ANDA is submitted. *See* 21 C.F.R. § 314.94(a)(12)(i)(A)(4)(i). Alternatively, the applicant may instead submit a statement that the ANDA is not seeking FDA approval for a method-of-use claimed in an Orange Book-listed patent (a "section viii statement"). 21 U.S.C. § 355(j)(2)(A)(viii).

Following a final court decision of infringement for a method of use claimed in an Orange Book-listed patent from which no appeal is or can be taken, FDA regulation provides that an ANDA applicant may either (1) forego approval for the patented method of use until the relevant patent expires, or (2) "amend[] its ANDA such that the applicant is no longer seeking approval for a method of use claimed

by the patent," i.e., convert the Paragraph IV certification to a section viii statement. 21 C.F.R. § 314.94(a)(12)(viii)(A).

II. FACTUAL AND PROCEDURAL BACKGROUND

A. Salix's Xifaxan

Salix Pharmaceuticals, Inc. ("Salix") is the holder of NDA No. 021361 for rifaximin tablets under the brand name Xifaxan, which is currently the only rifaximin product available on the market. Xifaxan 550 mg rifaximin tablets are indicated for the treatment of IBS-D in adults (the "IBS-D Indication") and for the reduction of the risk of overt HE recurrence in adults (the "HE Indication").

B. Norwich's ANDA and Salix's Patent Infringement Suit

Norwich submitted ANDA No. 214369 to FDA, seeking approval to market generic rifaximin 550 mg tablets for both the IBS-D and HE Indications ("Norwich's Original ANDA"). Norwich's Original ANDA contained Paragraph IV certifications for all 23 patents then listed in the Orange Book.

Salix subsequently filed a patent suit against Norwich in the District of Delaware under 35 U.S.C. § 271(e)(2) based on the Paragraph IV certifications. A four-day bench trial was held in March 2022. After post-trial briefing, the court ordered the parties to propose a final judgment based on the assumption that it would find Norwich's Original ANDA to infringe the HE Patents and that the Polymorph and IBS-D Patents are invalid. Appx3891. Norwich proposed an order that would delay the effective date of approval of the ANDA to the extent it seeks

approval for the HE Indication. Appx3905. Salix argued that Norwich's proposal was "improper because under § 271(e)(4)(A), the date of approval is tied to the drug product, not an indication." *Id.* at 2.

On August 10, 2022, the court issued its Final Judgment that the asserted polymorph and IBS-D patent claims are invalid as obvious, and that Norwich's Original ANDA seeking approval for the HE Indication would induce infringement of the HE Patents, which were not proven invalid. Appx51. Norwich has not appealed the infringement and validity holdings for the HE Patents.

The court also issued a Memorandum where it accepted Salix's argument that Section 271(e)(4)(A) requires an order tying the date of approval to the drug product. Appx48. It therefore rejected Norwich's proposal and ordered "that the effective date of any final approval by [FDA] of Norwich's ANDA No. 214369 is to be a date not earlier than the date of expiration of the last to expire" of the HE Patents, i.e., October 2 2029. Appx51.

Norwich subsequently submitted to FDA an amended ANDA with the HE Indication carved out and section viii statements in place of Paragraph IV certifications for the HE Patents (the "Amended ANDA"). On September 7, 2022, Norwich moved under Federal Rule of Civil Procedure 60(b)(5) and (6) to modify the Final Judgment to make it clear that it pertains to an ANDA with Paragraph IV

certifications to the HE Patents. Appx3997. On May 17, 2023, the court denied Norwich's motion. Appx52-56.

On June 2, 2023, FDA granted tentative approval to Norwich's Amended ANDA. *See* D.I. 23, Ex. A ("TA Letter"). FDA acknowledged that Norwich's Amended ANDA contains section viii statements regarding the HE Patents and that "these are method-of-use patents that do not claim any indication for which you are seeking approval under your ANDA." *Id.* at 3-4. FDA nevertheless stated that "final approval cannot be granted until October 2, 2029 as specified in the court order." *Id.* at 3.

C. Norwich Files Suit Against FDA

On June 5, 2023, Norwich filed suit in the District Court for the District of Columbia, seeking an order directing FDA to grant final approval to Norwich's Amended ANDA for the treatment of IBS-D. *Supra* p. 1. Norwich moved for a preliminary injunction that has been consolidated with a full consideration of the merits. On June 12, Salix moved to intervene in the action, and, on July 7, FDA moved for summary judgment. Briefing was completed on August 16, 2023, and oral argument is scheduled for October 6, 2023.

III. THE USE OF RIFAXIMIN TO TREAT IBS-D WAS WELL-KNOWN BEFORE FEBRUARY 2008.

IBS is characterized by symptoms including abdominal pain, bloating, frequency, urgency, gas, and changed bowel habits. Appx32 (citing Appx3139-

3141). "IBS may be caused, for example, by … changes in the microbiome in the colon or small intestine …." *Id*. There are three subtypes of IBS, and the IBS-D subtype comprises about one-third of IBS patients. *Id*. (citing Appx3143-3144).

"Rifaximin is a gut-selective antibiotic with negligible systemic absorption" and "a similar tolerability profile to placebo." Appx4639. When rifaximin became available in the U.S. in 2004, its use as a drug had been known for decades. Appx15-16 (citing Appx4900, Appx4902-4903), Appx26.

In 1999, Dr. Mark Pimentel filed for patents on methods of using rifaximin to treat IBS, which Salix licensed and listed on its Xifaxan label. Appx36 (citing Appx3138-3142, Appx5045-5073, Appx5074-5097), Appx2650, Appx4844, Appx3070-3071. In 2005, Salix hosted a conference where Pimentel discussed his research and use of rifaximin to treat more than 900 IBS patients. Appx36-37 (citing Appx3148-3149, Appx7344-7345). In 2006, Pimentel published a book recommending a protocol for treating IBS-D with rifaximin. Appx37 (citing Appx5794-5954, Appx3144-3145), Appx5886; Appx3366-3368. He also published an article, Pimentel 2006, Appx4639-4646, that disclosed administering rifaximin, 400 mg three times per day ("TID") for 10 days, to treat IBS patients (18-65 years of age) and achieving prolonged symptom relief. Appx37 (citing Appx4644).

Pimentel was not alone in using rifaximin. Appx3369-3371. Salix's expert, Dr. Philip Schoenfeld, admitted his use of rifaximin to treat IBS-D patients in 2007. Appx3068-3069. Indeed, by January 2008, 74% of surveyed gastroenterologists had prescribed rifaximin for IBS. Appx36 (citing Appx7185), Appx7186. Prior art, including Yang (Appx4952-4957), Cuoco (Appx4533-4539), and Barrett (Appx4799-4800), reported success in using rifaximin to treat IBS patients. Appx37, Appx43.

In 2005, Salix published a clinical study protocol – the RFIB2001 Protocol – for administering rifaximin 550 mg to 2200 mg per day for 14 days for the treatment of IBS-D. Appx37-38 (citing Appx7048-7055); Appx3174. In 2007, Salix announced (the "RFIB2001 Press Release") that "a 14-day course of rifaximin at 550 mg twice-a-day, provides a statistically significant improvement in both adequate relief of symptoms and adequate relief of bloating, compared to placebo." Appx38 (citing Appx7480-7483, Appx3177-3178).

IV. CRYSTALLINE RIFAXIMIN HAVING THE CLAIMED INHERENT PROPERTIES WAS KNOWN IN THE ART.

Crystalline rifaximin was first patented by Alphasigma's predecessors in the 1980s. *See* Appx4526-4532, Appx4617-4627. The currently asserted claims of the Polymorph Patents, which require the beta (β) crystalline form of rifaximin, merely claim what was already known in the art. The Cannata reference (Appx4526-4532) discloses crystalline rifaximin synthesized using a crystallization

solvent of ethanol and water, but without an aggressive drying step. *See, e.g.*, Appx3391-3393. Accordingly, as explained herein, this as-synthesized rifaximin would have been rifaximin β at least because it is a commonly produced and most stable polymorph of rifaximin. Thus, a POSA practicing the methods patented decades ago could – and did – produce rifaximin β. As further explained herein, this renders the Polymorph Patents obvious or, alternatively, inherently anticipated. *Infra* Section V.

SUMMARY OF THE ARGUMENT

I. THE DISTRICT COURT LEGALLY ERRED IN INTERPRETING SECTION 271(e)(4)(A) AND ABUSED ITS DISCRETION IN DENYING NORWICH'S RULE 60(B) MOTION.

The court legally erred by interpreting Section 271(e)(4)(A) of the Patent Act to require that the date of the ANDA approval must be tied to the "drug." In fact, the plain and ordinary meaning of the relevant statutory language requires courts to tie the approval date to the indication for which the ANDA seeks approval *when that indication is the source of the infringement*. Norwich's interpretation is also required to: (1) give meaning to rather than render redundant the relevant statutory language; (2) harmonize with rather than eviscerate the section viii mechanism; (3) harmonize with rather than abrogate basic principles of patent law; (4) further rather than obstruct Congress' central purpose of hastening the introduction of generic drugs; and (5) avoid the absurd result that approval of

Norwich's Amended ANDA is delayed by a Section 271(e)(4)(A) order that is based on infringement of a patent for which the ANDA *does not have a Paragraph IV certification* and that covers an indication for which the ANDA *does not seek approval*.

The court subsequently abused its discretion in denying Norwich's motion to modify the Final Judgment under Rule 60(b)(5) and (6). First, the court legally erred in holding that only money judgments can be "satisfied" under Rule 60(b)(5); the case law demonstrates that injunctions may also fall under this prong of the rule. Second, the court erred in failing to find that it is no longer equitable to apply the order under Rule 60(b)(5). Among other things, it incorrectly required that Norwich's ANDA amendment had to have been unforeseen; the case law applying this requirement is limited to requests to modify *consent* judgments. Finally, the court failed to even consider Norwich's motion under Rule 60(b)(6), despite Norwich having moved under the rule and argued for its applicability.

II. THE DISTRICT COURT CORRECTLY HELD THE IBS-D PATENTS OBVIOUS.

Salix tried its case on the facts and lost. It can point to no clear error in the court's determination that the asserted IBS-D Patent claims are obvious in view of Pimentel 2006 and the RFIB2001 Protocol.

First, the court correctly found that the RFIB2001 Press Release – issued by *Salix* – was prior art under pre-AIA Section 102(a) because "there was no

evidence" showing that the reference's relevant disclosures were derived from the work of any inventive entity. Salix failed to preserve this "derivation" issue in the Pretrial Order, failed to present testimony on the issue at trial, and failed to offer more than a conclusory, after-the-fact assertion in its post-trial brief. Salix's arguments on appeal fail to fill these evidentiary gaps. Regardless, even if the press release were not prior art, the evidence supports the court's conclusion and the alleged error is harmless.

Second, the court correctly found that the RFIB2001 Protocol discloses administering 550-2200 mg of rifaximin per day for 14 days for the treatment of IBS-D. Whether considered alone or in combination with Pimentel 2006, the claimed dose of 1650 mg per day for 14 days falls in the dosage range disclosed by the RFIB2001 Protocol. Contrary to Salix's assertion, the obviousness inquiry does not mandate efficacy data, and the claimed dose achieved what physicians already knew and the prior art disclosed. The court thus correctly found a reasonable expectation of success based on Norwich's evidence of "widespread off-label use," "positive results" reported in the prior art, and clinical studies. Salix lost on the facts at trial and fails to show any clear error on appeal.

III. THE DISTRICT COURT CORRECTLY HELD THE POLYMORPH PATENTS OBVIOUS.

The court, properly applying the factual record to the legal standards set forth in *Graham* and *KSR*, correctly found the Polymorph Patent claims obvious.

There is no special test for analyzing obviousness of polymorphs, and the *Pharmacyclics* and *Grunenthal* cases cited by Salix are distinguishable on the facts.

The court correctly found that Cannata disclosed crystalline rifaximin having antibacterial properties that would have motivated a POSA to consider it as a potential drug candidate. In view of regulatory guidance and a POSA's recognition that Cannata's process resulted in crystalline rifaximin with the potential to form a hydrate, the court correctly found that a POSA would have been motivated to perform routine testing to characterize the rifaximin prepared according to Cannata, including its water content and XRPD profile.

The court also correctly found that a POSA would have a reasonable expectation of successfully characterizing rifaximin β. The court recognized the inventor's admission that Cannata's process yields rifaximin β along with rifaximin α, δ, and ε. It also found that water content and XRPD peaks are inherent properties of a crystalline form. Based on Dr. Zaworotko's testimony, the court correctly found that a POSA would have reasonably identified rifaximin β having the claimed water content and XRPD profile because it was commonly produced and the most stable crystalline form. Accordingly, the court properly concluded that the Polymorph Patents are obvious.

Salix has not alleged any error by the court pertaining to the "pharmaceutically acceptable excipient or carrier" limitation of claim 36 of the '206 patent. Accordingly, the court's finding as to the obviousness of that claim should be affirmed.

IV. ALTERNATIVELY, THE DISTRICT COURT ERRED IN FAILING TO HOLD CLAIM 4 OF THE '199 PATENT INHERENTLY ANTICIPATED.

Even if claim 4 of the '199 patent were not obvious, the invalidity ruling should be affirmed on the alternative ground that the claim is inherently anticipated by Cannata. The inventor's own work reveals that practicing Cannata yields rifaximin β, α, δ, or ε, and mixtures thereof and demonstrates the undisputed natural relationship between these forms, i.e., that rifaximin α, δ, and ε cannot be formed without first preparing "wet rifaximin," the as-synthesized rifaximin that before drying necessarily contains rifaximin β. The court's failure to find inherency was therefore clearly erroneous.

ARGUMENT

I. STANDARD OF REVIEW

The Federal Circuit reviews *de novo* a district court's interpretation of statutory language. *See, e.g.*, *Syngenta Crop Prot., LLC v. Willowood, LLC*, 944 F.3d 1344, 1359 (Fed. Cir. 2019).

"Because denial of a Rule 60(b) motion is a procedural issue not unique to patent law," the Federal Circuit "appl[ies] the rule of the regional circuit where

appeals from the district court would normally lie[.]" *Amstar Corp. v. Envirotech Corp.*, 823 F.2d 1538, 1550 (Fed. Cir. 1987). The Third Circuit "review[s] the denial of Rule 60(b) relief for an abuse of discretion." *Coltec Indus., Inc. v. Hobgood*, 280 F.3d 262, 269 (3d Cir. 2002).

The Federal Circuit reviews a district court's inherent anticipation findings under the clearly erroneous standard. *Atlas Powder Co. v. IRECO Inc.*, 190 F.3d 1342, 1346 (Fed. Cir. 1999).

"An abuse of discretion exists where the District Court's decision rests upon a clearly erroneous finding of fact, an errant conclusion of law, or an improper application of law to fact." *Meyer v. CUNA Mut. Ins. Soc.*, 648 F.3d 154, 169 (3d Cir. 2011) (citation omitted).

II. THE DISTRICT COURT LEGALLY ERRED IN FAILING TO REFERENCE THE HE INDICATION IN THE 271(e) ORDER.

The court legally erred by interpreting the remedy provision in Section 271(e)(4)(A) to require that the date of the ANDA approval in the mandated order to be tied solely to the "drug," which it implemented by tying the approval date to the ANDA number. Appx51. The language of the statutory provision requires courts to tie the restriction on FDA approval to the indication for which the ANDA seeks approval *when that indication is the source of the infringement under Section 271(e)(2)(A)*. That is also required to harmonize the remedy section with the section viii mechanism in the Hatch-Waxman Act and

basic principles of patent law, and to avoid the absurd result that the 271(e) order here serves to delay the approval of an ANDA that does not contain a Paragraph IV certification to any valid and infringed patent.

A. Only Norwich's Interpretation Imbues the Statutory Language With Meaning.

In rejecting Norwich's proposal that the 271(e) order make clear that it only applies to an ANDA seeking approval for the infringing HE Indication, the court simply quoted the statutory language: "the court shall order the effective date of any approval of the drug … involved in the infringement to be a date which is not earlier than the date of the expiration of the patent which has been infringed." Appx48 (quoting 35 U.S.C. § 271(e)(4)). Thus, the court adopted Salix's contention that Section 271(e)(4)(A) ties "the date of approval … to the drug product, not an indication." Appx3893.

This interpretation of the statute reduces the term "involved in the infringement" to an identifier of the drug to which the order should be directed. As a mere identifier, however, the term is wholly redundant because the relevant drug (and drug application) is already identified in Section 271(e)(2)(A), which itself is explicitly referenced in the first sentence of Section 271(e)(4)(A):

Section 271(e)(2)(A)	Section 271(e)(4)(A)
(2) It shall be an act of infringement to submit — (A) an [ANDA] … for a drug claimed in a patent or the use of which is claimed in a patent ….	(4) For an act of infringement described in paragraph (2) — (A) the court shall order the effective date of any approval of the drug … involved in the infringement to be a date which is not earlier than the date of the expiration of the [infringed] patent … .

35 U.S.C. § 271(e)(2)(A) and (4)(A).

It is "a fundamental canon of statutory construction that the words of a statute must be read in their context and with a view to their place in the overall statutory scheme." *FDA v. Brown & Williamson Tobacco Corp.*, 529 U.S. 120, 133 (2000) (quotation omitted). Here, Section 271(e)(4)(A) must be read in context with the definition of infringement in Section 271(e)(2)(A), which it expressly references. As is apparent, a court cannot reach the remedy in Section 271(e)(4)(A) until it has found infringement under Section 271(e)(2)(A), and it cannot find infringement without identifying that which is infringed. The relevant drug is therefore fully identified *before* the term "involved in the infringement" occurs in Section 271(e)(4)(A) and there is no need to identify it a second time.

An interpretation that renders statutory language redundant or mere surplusage is contrary to the "cardinal principle of statutory construction" of "giv[ing] effect, if possible, to every clause and word of a statute." *Duncan v. Walker*, 533 U.S. 167, 174 (2001) (quotation omitted). Instead, "a statute ought, upon the whole, to be so construed that, if it can be prevented, no clause, sentence,

or word shall be superfluous, void, or insignificant." *Id.* (citation omitted). The interpretation of "involved in the infringement" as merely an identifier fails this maxim and must be rejected. *See, e.g., Sharp v. United States*, 580 F.3d 1234, 1238 (Fed. Cir. 2009) (rejecting statutory interpretation because courts "should avoid rendering any of the statutory text meaningless or as mere surplusage").

Properly construed, the term is not an identifier but rather a *qualifier* or *restriction* on the scope of the 271(e) order. Section 271(e)(2)(A) provides that an ANDA infringes if it is for a drug *or* a use (i.e., an approved indication)[1] claimed in a patent. Conversely, as this Court has put it, "an ANDA seeking to market a drug not covered by a composition patent for unpatented methods of treatment cannot infringe under § 271(e)(2)." *AstraZeneca Pharms. LP v. Apotex Corp.*, 669 F.3d 1370, 1379 (Fed. Cir. 2012). Thus, the "act of infringement" for which Section 271(e)(4)(A) provides a remedy can refer to infringement of a patent claiming the drug itself, infringement of a method patent claiming the applied-for indication, or both.

When such infringement has occurred, Section 271(e)(4)(A) provides that the court shall "order the effective date of any approval of *the drug … involved in the infringement*" to not be earlier than expiration of the infringed patent.

[1] FDA does not approve a drug *per se* but rather a drug for one or more indications demonstrated to be safe and effective. *Infra* pp. 19-20.

35 U.S.C. § 271(e)(4)(A) (emphasis added). In other words, the statute mandates that the court order be directed not merely to "the drug" but to the drug "involved in the infringement." As discussed, "the infringement" in Section 271(e)(2)(A) pertains either to the drug described in the ANDA or the use of that drug for which the ANDA seeks approval, i.e., the indication. *See Johnson v. United States*, 559 U.S. 133, 139 (2010) ("Ultimately, context determines meaning"). The term "involved in the infringement" therefore serves as a qualifier on the 271(e) order that ensures that the order is tailored to the actual act of infringement.

Here, the court found induced infringement under Section 271(e)(2)(A) solely because Norwich's Original ANDA sought approval for the HE Indication. *Supra* pp. 4-5. Thus, rifaximin – "the drug" – is only "involved in the infringement" *when it is used for the HE Indication.* Conversely, rifaximin is not "involved in the infringement" when, for example, it is sold or used for the IBS-D Indication. To comply with the statutory requirements for the 271(e) order, therefore, the court had to specify that the approval date pertains to Norwich's ANDA seeking approval for the infringing HE Indication.

B. Only Norwich's Interpretation Maintains Consistency With Other Sections of the Act and Its Overarching Purpose.

"When interpreting a statute, the court will not look merely to a particular clause in which general words may be used, but will take in connection with it the whole statute (or statutes on the same subject) and the objects and policy of the

law, as indicated by its various provisions, and give it such a construction as will carry into execution the will of the Legislature." *Warner-Lambert Co. v. Apotex Corp.*, 316 F.3d 1348, 1355 (Fed. Cir. 2003). *See also Johnson v. United States*, 529 U.S. 694, 710 n.10 (2000) ("Our obligation is to give effect to congressional purpose so long as the congressional language does not itself bar that result."). As discussed above, only Norwich's interpretation of the term imbues it with meaning. *Supra* pp. 15-18. Furthermore, only Norwich's interpretation is consistent with the section viii mechanism in the Act and its overarching goal of hastening the introduction of generic drugs.

Congress enacted the Hatch-Waxman Act with the goal of bringing "'generic … drugs to market as quickly as possible.'" *Teva Pharms. USA, Inc. v. Novartis Pharms. Corp.*, 482 F.3d 1330, 1344 (Fed. Cir. 2007) (quoting Sen. Kennedy Remarks, 149 Cong. Rec. S15885 (Nov. 25, 2003)). *See also In re Barr Lab'ys, Inc.*, 930 F.2d 72, 76 (D.C. Cir. 1991) ("Congress sought to get generic drugs into the hands of patients at reasonable prices – fast."). Congress accomplished this goal in part by providing an avenue for ANDA filers to obtain approval for indications that are *not* covered by any valid patents listed in the Orange Book.

"FDA does not grant across-the-board approval to market a drug [but rather] to make, use, and sell a drug for a specific purpose for which that drug has

been demonstrated to be safe and efficacious." *Warner-Lambert*, 316 F.3d at 1356. When enacting the Hatch-Waxman Act, therefore, "Congress contemplated the possibility that there could be more than one approved indication for a given drug, and that an ANDA applicant can seek approval to label and market the drug for fewer than all of those indications." *Id.* at 1362. Congress consequently provided ANDA applicants the option to not seek approval for a patented indication by submitting a section viii statement rather than a Paragraph IV or other patent certification for listed method-of-use patents. 21 U.S.C. § 355(j)(2)(A)(viii). In sum, "[t]he Hatch-Waxman Amendments authorize the FDA to approve the marketing of a generic drug for particular unpatented uses; and section viii provides the mechanism for a generic company to identify those uses, so that a product with a label matching them can quickly come to market." *Caraco Pharm. Lab'ys, Ltd. v. Novo Nordisk A/S*, 566 U.S. 399, 415 (2012).

Congress did not place any temporal limitation on an ANDA applicant's submission of a section viii statement. FDA therefore permits an ANDA applicant at any time, including "*[a]fter [a] finding of infringement*," to "amend[] its ANDA such that the applicant is no longer seeking approval for a method of use claimed by the patent" by converting a Paragraph IV certification to a section viii statement. 21 C.F.R. § 314.94(a)(12)(viii)(A). Furthermore, an ANDA with a

section viii statement may be approved "immediately." 21 C.F.R. § 314.107(b)(1)(ii).

Here, Norwich prevailed on its challenge to the IBS-D and Polymorph Patents, and utilized the section viii mechanism to remove the infringing HE Indication and Paragraph IV certifications to the HE Patents from its ANDA. *Supra* pp. 4-6. Under a straightforward application of the section viii provision and FDA regulations, therefore, there can be no patent barrier to FDA approval of Norwich's Amended ANDA. FDA nevertheless believes itself to be blocked from approving Norwich's Amended ANDA by the court's 271(e) order. *Supra* p. 6. Thus, the interpretation of Section 271(e)(4)(A) urged by Salix and adopted by the court leads to the absurd result that it requires courts to issue 271(e) orders that FDA deems to be blocking it from approving ANDAs that do not seek approval for an indication covered by a valid Orange-Book patent. That interpretation does the opposite of "carry[ing] into execution the will of the Legislature" and must be rejected. *Warner-Lambert*, 316 F.3d at 1355.

Furthermore, only Norwich's interpretation is consistent with the animating purpose of the Act of bringing generics to market "as quickly as possible.'" *Teva*, 482 F.3d at 1344. As demonstrated by the facts of this case, FDA reads the court's order as delaying it from approving Norwich's Amended ANDA, whereas an order following a proper interpretation of the statutory language would not.

Unwarranted delay of approval could also occur in other situations. Take, for example, the case where a generic company files an ANDA seeking approval for two distinct indications covered by different method-of-use patents with different expiration dates. The generic applicant submits Paragraph IV patent certifications but fails to prove at trial that the patents are not infringed or invalid. Unless the court fashions a Section 271(e)(4)(A) order that differentiates between the two indications and patent expiration dates, FDA would not approve the indication covered by the earlier-expiring patent until expiration of the later-expiring patent.

Perhaps recognizing the absurdity of a Section 271(e)(4)(A) order delaying FDA from approving an ANDA for an indication that is not covered by a patent, the court has previously issued an order that distinguished between indications in a case with facts that mirror the above example. In a 271(e) order from 2017, the court specified that FDA approval of West-Ward's "ANDA No. 207486 *for the Everolimus RCC Indication*" could not be earlier than the expiration of one patent while approval of "ANDA No. 207486 *for the Everolimus PNET Indication*" could not be earlier than the expiration of a second later-expiring patent. Appx3925-3926 (emphasis added).[2] And following that order, West-Ward did exactly as

[2] At least one other district judge has issued a Section 271(e)(4)(A) order specifying the relevant indication. Final Judgment, *Genzyme Corp. and Sanofi-Aventis U.S. LLC v. Zydus Pharms. (USA) Inc.*, No. 16-00540 (D. Del. August 21,

Norwich has done here and amended its ANDA post-judgment to carve out the indication covered by the later-expiring patent and substitute a section viii for the Paragraph IV certification in its original ANDA. *See* FDA letter to Hikma Pharmaceuticals USA Inc., granting tentative approval to ANDA 207486, https://www.accessdata.fda.gov/drugsatfda_docs/appletter/2019/207486Orig1s000TAltr.pdf (last visited Aug. 22, 2023).[3] Section 271(e)(4)(A) required the court to similarly limit the order here, thereby assuring FDA approval of Norwich's Amended ANDA just as it did for West-Ward's amended ANDA.

C. Only Norwich's Interpretation Is Consistent With Fundamental Principles of Patent Law.

Although the Hatch-Waxman Amendments created what has been called "a highly artificial act of infringement that consists of submitting an ANDA," *Eli Lilly & Co. v. Medtronic, Inc.*, 496 U.S. 661, 678 (1990), there is no basis in the Amendments themselves or any surrounding legislative history to suggest that Congress intended to alter or abrogate any settled principles of patent law. That

2018), D.I. 109. The large majority of Section 271(e)(4)(A) orders involve infringement of a patent for the drug or drug product.

[3] West-Ward became Hikma in 2018. *See* Press Release, Hikma Pharmaceuticals PLC, https://www.hikma.com/newsroom/article-i3042-west-ward-pharmaceuticals-now-hikma-in-the-us-as-part-of-global-rebranding/ (last visited Aug. 22, 2023).

the interpretation of Section 271(e)(4)(A) urged by Salix and adopted by the court would nevertheless have this effect is yet another reason for its rejection.

1. Injunctions Must Be Specifically Tailored to the Infringing Conduct.

As the court made clear, "[t]he scope of my ruling is that the HE patents are not invalid, and that the HE indication would infringe the HE patents." Appx48. This in contrast to the IBS-D and polymorph claims, which the court held invalid and thus not infringed. Appx51.

There is no statutory or legal justification for a Section 271(e)(4)(A) order that delays the approval of an ANDA for any reason other than the basis for which the ANDA infringes a patent. On the contrary, it is "a general rule [that] a court may not enjoin products that have not been found by the jury to infringe the patents-in-suit, and therefore any injunction[4] should be specifically tailored to comport with the jury's findings." *Durel Corp. v. Sylvania, Inc.*, No. 95-1750, 2000 WL 33687212, at *1 (D. Ariz. Apr. 13, 2000) (citing *Square Liner 360, Inc. v. Chisum*, 691 F.2d 362, 378 (8th Cir. 1982)). *See also Joy Techs., Inc. v. Flakt*,

[4] Although a Section 271(e)(4)(A) order is a statutory remedy "it provides relief in the nature of an injunction…." *SmithKline Beecham Corp. v. Apotex Corp.*, 247 F. Supp. 2d 1011, 1050 (N.D. Ill. 2003), *aff'd*, 365 F.3d 1306 (Fed. Cir. 2004), *opinion vacated on reh'g en banc*, 403 F.3d 1328 (Fed. Cir. 2005), *and superseded*, 403 F.3d 1331 (Fed. Cir. 2005), *and aff'd on other grounds*, 403 F.3d 1331 (Fed. Cir. 2005). It is not "substantively different from a permanent injunction in traditional patent litigation." *Actavis Lab'ys, FL, Inc. v. United States*, 161 Fed. Cl. 334, 364 (2022) (internal citations omitted).

Inc., 6 F.3d 770, 777 (Fed. Cir. 1993) (stating that "[j]udicial restraint of lawful competitive activities … must be avoided" and vacating and remanding injunction to narrow scope precluding non-infringing activities).

There can be no dispute that a Section 271(e)(4)(A) order that references the HE Indication is more tailored to the infringement finding here than the order the court issued. Indeed, FDA has taken the position that the court's order is so broad that it prevents FDA from approving Norwich's Amended ANDA *despite* acknowledging that it does not seek approval for the HE Indication or have Paragraph IV certifications to the HE Patents. *Supra* p. 6. By way of analogy, this is effectively like enjoining Ford from selling all Ford Mustangs based on infringement of a patent covering only the intermittent windshield wipers, even after the Mustangs are redesigned to not use intermittent windshield wipers. Congress cannot have intended for the Hatch-Waxman Act to so grossly distort this basic tenet of patent injunctions.

2. Patent Law Encourages Infringers to Design Around the Infringement.

It is a truism that "patent law encourages competitors to design or invent around existing patents." *WMS Gaming, Inc. v. Int'l Game Tech.*, 184 F.3d 1339, 1355 (Fed. Cir. 1999). Thus, infringers that are the subject of an injunction can go to market with a product that is redesigned to no longer infringe. There is no indication that Congress intended to foreclose an infringer's ability to do similarly

in the Hatch-Waxman context. On the contrary, the section viii provision in the Act provides the mechanism for carving out and foregoing FDA approval for an infringing indication. This is exactly what Norwich's Amended ANDA accomplishes, yet FDA has determined that it remains blocked from approving it by the court's Section 271(e) order. Again, therefore, the interpretation of Section 271(e)(4)(A) urged by Salix and adopted by the court is contrary to a fundamental principle of patent law.

D. The District Court's Order Leads to Absurd Outcomes and Is Contrary to Clear Congressional Intent.

The Supreme Court has explained that "interpretations of a statute which would produce absurd results are to be avoided if alternative interpretations consistent with the legislative purpose are available." *Griffin v. Oceanic Contractors, Inc.*, 458 U.S. 564, 575 (1982). *See also Pub. Citizen v. DOJ*, 491 U.S. 440, 455 (1989) ("Looking beyond the naked text for guidance is perfectly proper when the result it apparently decrees is difficult to fathom or where it seems inconsistent with Congress' intention.") (quotation marks and citation omitted). Consequently, this Court should adopt Norwich's interpretation to avoid the absurd results discussed above in the circumstances present here, i.e., eviscerating the section viii mechanism, abrogating standard principles of patent law, and thwarting the Act's central goal of hastening the introduction of generic drugs. *Supra* pp. 14-26.

III. THE DISTRICT COURT ABUSED ITS DISCRETION IN DENYING NORWICH'S MOTION TO MODIFY THE JUDGMENT.

Following the entry of Final Judgment, and having decided not to appeal the merits of the infringement decision with respect to the HE Patents, Norwich utilized the section viii framework and implementing FDA regulation to amend the ANDA by carving out the infringing HE Indication and substituting section viii statements for the Paragraph IV certifications to the HE Patents. *Supra* pp. 4-6. To avoid the possibility that FDA would incorrectly apply the Section 271(e)(A)(4) order to the Amended ANDA, Norwich also asked the court to modify that order under Rule 60(b)(5) and (6) of the Federal Rules of Civil Procedure to make it abundantly clear that it applies only to the ANDA with Paragraph IV certifications to the HE Patents. The court's denial of Norwich's motion was an abuse of discretion.

A. The District Court Legally Erred in Holding That Only a Money Judgment Can Be "Satisfied" Under Rule 60(b)(5).

Among the grounds for relief under Rule 60(b)(5) is that "the judgment has been satisfied, released, or discharged." Fed. R. Civ. P. 60(b)(5). By amending the ANDA to remove the HE Indication and corresponding Paragraph IV certifications from the ANDA, Norwich guaranteed that FDA will not approve any Norwich ANDA with the infringing HE Indication until after the expiration of the HE Patents, just as the Section 271(e) order required. *See supra* pp. 4-6. Norwich

thus provided the entire relief that Salix sought in its infringement claim under Section 271(e) relating to the HE Patents. As such, Norwich's ANDA amendment satisfied the Final Judgment.

The court summarily dismissed Norwich's argument, stating that "I think it is pretty clear that the 'satisfied, released, or discharged' language [in Rule 60(b)(5)] is talking about money, and is therefore inapplicable." Appx53. The court cited no authority for this legally erroneous proposition. In fact, "[u]nder Rule 60(b)(5), the court may relieve a party of the obligations of *an injunction* where its conditions have been satisfied." *N. Carolina All. for Transp. Reform, Inc. v. U.S. Dep't of Transp.*, 713 F. Supp. 2d 491, 504 (M.D.N.C. 2010) (emphasis added) (granting motion to dissolve injunctive provisions in an order). *See also Sierra Club v. Mason*, 365 F. Supp. 47, 49 (D. Conn. 1973) (granting motion to vacate injunction under Rule 60(b)(5) when condition in injunction had been fulfilled); *All. for Wild Rockies v. Kruger*, 15 F. Supp. 3d 1052, 1056 (D. Mont. 2014), *aff'd sub nom. All. for the Wild Rockies v. Krueger*, 664 F. App'x 674 (9th Cir. 2016) (granting motion to dissolve injunction under Rule 60(b)(5) when defendants had "satisfied" the judgment and injunction).

The court's summary denial was thus premised on legal error. When properly considered, Norwich's Amended ANDA satisfies the Final Judgment,

which this Court should therefore revise as Norwich requested in its motion. Appx3999-4000.

B. The District Court Also Erred in Failing to Find That It Is No Longer Equitable to Apply the Order Prospectively.

Rule 60(b)(5) additionally provides for relief from a final judgment "if applying it prospectively is no longer equitable." Fed. R. Civ. P. 60(b)(5). As such, the rule "provides a means by which a party can ask a court to modify or vacate a judgment or order if a significant change either in factual conditions or in law renders continued enforcement detrimental to the public interest." *Horne v. Flores*, 557 U.S. 433, 447 (2009). "The party seeking relief bears the burden of establishing that changed circumstances warrant relief, but once a party carries this burden, a court abuses its discretion when it refuses to modify an injunction [ ] in light of such changes." *Id*.

Here, Norwich's amendment of its ANDA changed the operative facts that gave rise to the Section 271(e) order in the Final Judgment. With the amendment, Norwich no longer sought approval for the HE Indication – the sole basis for the infringement finding and Section 271(e) order. Given the possibility that FDA would nevertheless incorrectly interpret the order as applying to the Amended ANDA (as it has now done), the continued enforcement of the order was and is "detrimental to the public interest." *Horne*, 557 U.S. at 447. *See also WMS Gaming*, 184 F.3d at 1355 ("[P]atent law encourages competitors to design or

invent around existing patents."). As discussed above, Congress intended for the Act to hasten the introduction of generic drugs; not delay ANDAs that do not seek approval for any indication covered by a patent. *Supra* p. 18-23. The court's denial of this ground of Norwich's motion was legal error and abuse of discretion.

First, citing *Rufo v. Inmates of Suffolk Cnty. Jail*, 502 U.S. 367, 383 (1992), the court held that this prong of Rule 60(b)(5) only applies when the change in circumstances were not anticipated when the final judgment was entered. Appx53. The court failed to appreciate, however, that *Rufo* and cases like it all concern *consent* decrees or *consent* judgments. *Rufo*, 502 U.S. at 383. As *Rufo* discusses, a party that seeks to modify a decree or judgment *that it itself had consented to* "would have to satisfy a heavy burden" to later obtain relief from that decree or judgment. *Id.* at 385.

Conversely, in cases involving injunctions rather than consent decrees, courts do not place emphasis on whether the change in circumstances was unexpected. In *Stone v. Trump*, for example, the movant had caused the changed circumstances justifying the dissolution of a preliminary injunction under Rule 60(b)(5) by revoking the memorandum that formed the basis for the injunction. 400 F. Supp. 3d at 332. In line with the relevant case law, the court considered whether it was "in the public interest" to continue the injunction, *id.* at 333, and not whether revoking the memorandum was anticipated or foreseeable.

Similarly, in *Sierra Club v. USDA*, the court found that "the public interest is served" by dissolving an injunction under Rule 60(b)(5) when the movant had "embarked on an entirely new forest planning process" and left behind the plans upon which the injunction had been based. No. 94-4061, 2013 WL 811672, at *17, *20 (S.D. Ill. Mar. 5, 2013). This case is more akin to *Stone* and *Sierra Club* than *Rufo* and its progeny, and it was legal error for the court to impose the "heavy burden" that the changed circumstances should be unforeseeable.

Second, the court erred in its analysis of "equitableness." Appx54. It deemed the harm to the public interest from a delay of approval of Norwich's Amended ANDA "a bit speculative" in the absence of certainty as to "if or when" FDA would give such approval. *Id.* But there was no reason to doubt that FDA would provide such approval much sooner than October 2, 2029, the date in the Section 271(e) order. Norwich submitted the ANDA in December of 2019, and the median time for FDA to grant final approval is currently less than 2 years. See https://www.fda.gov/industry/generic-drug-user-fee-amendments/generic-drugs-program-monthly-and-quarterly-activities-report, (last visited on Aug. 22, 2023). In fact, FDA provided tentative approval of the Amended ANDA on June 2, 2023, establishing that it is eligible for final approval but for FDA's interpretation of the 271(e) order. TA Letter. The court's reference to Norwich's "strategic choices" is also misplaced. As already discussed, FDA's implementation of the Hatch-

Waxman Act explicitly provides for amendment of an ANDA to carve out an infringing indication *after* a final judgment of infringement. *Supra* pp. 2-4. It is an abuse of discretion to impede Norwich from following the pathway that Congress and FDA provided in the service of the public interest.

Third, granting modification of the Final Judgment is not tantamount to "relitigation of issues that have been resolved by the judgment." Appx55. On the contrary, Norwich's modification would only make the infringement judgment more precisely expressed in the 271(e) order. *Allergan, Inc. v. Sandoz*, the single opinion cited by the court, has no bearing on Norwich's motion. *Id*. In that case, the ANDA applicant requested that the court "make a determination that Sandoz's amended ANDA does not infringe" the relevant claim. No. 09-200, 2013 WL 6253669, at *2 (E.D. Tex. Dec. 3, 2013), *aff'd*, 587 F. App'x 657 (Fed. Cir. 2014). *See also id.* at *3 ("Sandoz petitions the Court for a ruling that its amended ANDA, which was submitted after the Federal Circuit's ruling, does not infringe ….").
Norwich, by contrast, does not seek any determination – or "relitigation" – of any finding pertaining to the patent merits. Moreover, *Allergan* was decided before FDA issued its regulation permitting the amendment of an ANDA and submission of a section viii statement after a finding of infringement. 21 C.F.R. § 314.94(a)(12)(viii)(A); 81 Fed. Reg. 18,766 (Oct. 6, 2016).

Finally, the court improperly used its discretion when finding that "it just seems wrong to me that Defendant can litigate a case through trial and final judgment based on a particular ANDA, and then, after final judgment, change the ANDA to what it wishes it had started with, and win in a summary proceeding." Appx56. It was arbitrary to let subjective feelings of wrongness trump the simple fact that Norwich has done nothing more than follow the path established by Congress and FDA to further the goal of hastening the introduction of generic drugs. Furthermore, that path does not represent a "win in a summary proceeding." *Id.* On the contrary, Norwich had to relinquish its right to appeal the validity and infringement finding for the HE Patents, and forgo the opportunity to obtain approval for the HE Indication. If anything, the court's denial of Norwich's motion is tantamount to a summary win for Salix that Norwich's Amended ANDA somehow infringes the HE Patents, an assertion that Salix has not even made.

Norwich has demonstrated that it is "no longer equitable" to apply the 271(e) order in the Final Judgement prospectively, especially in view of FDA's interpretation of the order as blocking approval of Norwich's Amended ANDA. The court abused its discretion in failing to modify the order, and this Court should correct that error and order the modification that Norwich sought. Appx3999-4000.

C. The District Court Further Erred in Failing to Even Consider Norwich's Motion Under Rule 60(b)(6).

Norwich also sought relief under Rule 60(b)(6). DI 206 at 6, 17-18, DI 215 at 10. "Rule 60(b)(6) is a catch-all provision that authorizes a court to grant relief from a final judgment for 'any … reason' other than those listed elsewhere in the Rule." *Cox v. Horn*, 757 F.3d 113, 120 (3d Cir. 2014). Courts properly exercise their broad powers under Rule 60(b)(6) in "extraordinary circumstances where, without such relief, an extreme and unexpected hardship would occur." *Id.* at 120.

The court failed to consider Norwich's motion under Rule 60(b)(6), stating only that Norwich "was primarily relying upon Rule 60(b)(5)." Appx52. Although the majority of Norwich's briefs discussed relief under Rule 60(b)(5), Norwich plainly stated that it sought relief under Rule 60(b)(6), provided the relevant factors courts should consider, and argued that those factors support relief in this case. Appx3980, Appx3991-3992, Appx4225. The court thus abused its discretion in failing to consider Norwich's request under Rule 60(b)(6). *See Venture Indus. Corp. v. Autoliv ASP, Inc.*, 457 F.3d 1322, 1332 (Fed. Cir. 2006) (vacating denial of motion when the court failed to consider a ground that was "properly raised" in Rule 60(b)(3) motion).

These are certainly "extraordinary circumstances." *Cox*, 757 F.3d at 120. Norwich is not aware of any other instance where the approval of an ANDA is blocked by a Section 271(e) order that is based on infringement of a patent that the

ANDA provides a section viii statement for and that covers a use for which the ANDA is *not* seeking approval. Furthermore, Norwich has earned the extremely valuable opportunity to be the first to offer generic rifaximin tablets for the treatment of IBS-D by defeating Salix's patents covering the IBS-D Indication and the polymorphic form of rifaximin. *See* D.I. 23 at 2-3, 6-7. Losing that opportunity will impose severe and unrecoverable costs on Norwich, *see id.* at 10-12, and thus constitute "an extreme and unexpected hardship." *Cox*, 757 F.3d at 120.

Norwich respectfully submits that the issues are sufficiently clear and the harm to Norwich from further delay sufficiently significant that this Court should reverse rather than remand. *See, e.g., Medichem, S.A. v. Rolabo, S.L.*, 437 F.3d 1157, 1173 (Fed. Cir. 2006) (reversing when "the facts of the case admit of only one conclusion as a matter of law"). Specifically, the Court should reverse the denial of Norwich's motion and order the modification of the Final Judgment that Norwich sought. Appx3999-4000.

IV. THE DISTRICT COURT CORRECTLY HELD THE IBS-D PATENTS OBVIOUS.

At bottom, Salix disagrees with the court's resolution of two fact disputes in finding the asserted IBS-D Patents obvious. None of Salix's arguments come close to establishing clear and reversible error in the court's findings that "there was no evidence" that a press release issued *by Salix* was derived from the inventors' work

or that the prior art disclosed a rifaximin dosage range that encompassed the claimed dosage amount. *Adapt Pharma Operations Ltd. v. Teva Pharms. USA, Inc*., 25 F.4th 1354, 1364 (Fed. Cir. 2022) ("A factual finding is only clearly erroneous if … [this Court is] left with the definite and firm conviction that a mistake has been made.").

The overwhelming evidence presented at trial supports the court's determination that "Pimentel 2006 in light of the RFIB 2001 Protocol renders the asserted [IBS-D patent] claims obvious." Appx37. Pimentel 2006 "reported sustained improvement in IBS symptoms for patients aged 18-65 for at least 10 weeks on a 400 mg TID, 10-day regimen." Appx38. "The RFIB 2001 Protocol included no upper age limit, a 14-day dosing regimen of 550 mg to 2200 mg per day, and the treatment of patients with IBS-D in particular." Appx38. The court found that "a POSA would have been motivated to combine Pimentel 2006 with the RFIB 2001 Protocol and would have had a reasonable expectation of success." Appx38

Tellingly, Salix does not dispute that POSAs had used rifaximin off-label to treat IBS-D before February 2008. Br. 17-18, Appx3369-3371. Its own expert had done so. Appx3068-3069. Salix also does not challenge the court's motivation findings, or assert any theory based on an unexpected result or a teaching away. Administering rifaximin 550 mg TID per day for 14 days to treat IBS-D patients

achieved what the prior art had reported and what doctors and patients had recognized.

Thus, the court's obviousness determination should be affirmed.

A. The RFIB2001 Press Release Is Prior Art.

The court did not clearly err in finding that the RFIB2001 Press Release is prior art. The parties stipulated in the Pretrial Order that, "[t]o qualify as prior art under pre-AIA 35 U.S.C. § 102(a) to the Asserted IBS-D Patents, the art must be dated prior to February 26, 2008." Appx1443 ¶ 130. A publication is a reference under Section 102(a) if it describes "the work of another." *In re Katz*, 687 F.2d 450, 454 (C.C.P.A. 1982).

There is no dispute that the 2007 RFIB2001 Press Release was issued by Salix rather than by any inventor. *See* Appx7480, Appx38, Br. 14. Furthermore, there is nothing in "the portions of the reference relied on as prior art, and the subject matter of the claims in question," that facially "represent the work of a common inventive entity." *EmeraChem Holdings, LLC v. Volkswagen Grp. of Am., Inc*., 859 F.3d 1341, 1345 (Fed. Cir. 2017). "Salix" is a corporation, Appx1427-1428, whereas the '569 patent lists William Forbes and Lorin Johnson as inventors, and the '667 patent lists William Forbes and Enoch Bortey, Appx1432-1433. There is no indication that *Salix's* knowledge or work, as disclosed in the reference, was derived from either named inventive entity. *In re*

Facius, 408 F.2d 1396, 1405-07 (CCPA 1969) (requiring evidence of derivation by reference and inventorship of the disclosure). Nor does the reference indicate that Forbes, Johnson, or Bortey, alone or collectively, conceived of the RFIB2001 Protocol. Appx7480-7481. On the contrary, it states that, "[i]n this particular trial *Salix*, in consultation with the *GI Division of the FDA*, designed and used a rigorous protocol … ." *Id*. (emphasis added).

Furthermore, Salix asserts that the IBS-D Patents claim a dosing regimen (i.e., 550 mg TID for 14 days) that is different than that (i.e., 550 mg BID for 14 days) reported in the RFIB2001 Press Release. Appx3321-3322. Salix does not dispute that the use of rifaximin to treat IBS-D was known before September 2007. Br. 13, 17. *LSI Corp. v. Regents of Univ. of Minn.,* 43 F.4th 1349, 1356-57 (Fed. Cir. 2022) (reproducing information is not inventive). This is not a case, therefore, where the claimed invention is disclosed in the disputed reference. *Contra* Br. 32-33.

In the Pretrial Order, Salix failed to preserve any argument that the disclosures of the RFIB2001 Press Release were "derived" from the inventors' work. Thus, it is waived. Appx41. "Issues of fact to be tried must be stated in the Final Pretrial Order to be preserved as issues for trial. If they are not so preserved, they are waived." *Prometheus Lab'ys Inc. v. Roxane Lab'ys, Inc*., No. 11-1241, 2014 WL 12607728, at *19-20 n.22 (D.N.J. May 21, 2014) (citing *Petree v. Victor*

Fluid Power, Inc., 831 F.2d 1191, 1194 (3d Cir. 1987)). Like the unexpected result issue found waived in *Prometheus*, Salix bore the burden of production on a derivation theory and thus had to disclose the issue in the Pretrial Order. It did not. Appx41. Salix's listing of this reference on a generic list of references that questioned whether Norwich has proven "qualify as prior art" is insufficient. Br. 36.

Regardless, Salix did not present evidence at trial concerning the conception of any disclosure in the RFIB2001 Press Release. Appx41-42. *Allergan, Inc. v. Apotex Inc*., 754 F.3d 952, 969 (Fed. Cir. 2014) (no evidence that the inventor "was responsible for directing the production of either article's content, which includes the design, trial, and analysis of results"). Nor did Salix present evidence concerning conception of the claimed invention. Consequently, Salix's one sentence post-trial argument, even if not waived, cites no record evidence of derivation. Br. 37 (citing Appx3787 ¶ 183, Appx3744).

The court correctly found that "there was no evidence upon which to make a factual finding that the press release was derived from the inventor's work." Appx41-42. The evidence thus "could not support a legal conclusion" that the RFIB2001 Press Release discloses the inventors' work. *Allergan, Inc.*, 754 F.3d at 969-70.

Neither of Salix's appeal arguments can provide the missing evidence. Br. 34-35. Salix cites a partial quote by Forbes – in his corporate capacity as "Vice President, Research and Development, Salix" – referencing "our" study. Br. 34. This establishes only that Forbes was aware of the information in September 2007, but cannot support an inference that the reference discloses his work. Moreover, Forbes' use of "our" or "we" refers to "Salix" as a corporate entity as demonstrated by his statement that "[w]e are extremely pleased with the outcome of our … study of rifaximin*, which we market in the U.S. under the trade name Xifaxan*…." Appx7480. It was Salix, not Forbes or any other individual, that "market[ed]" Xifaxan and conducted the "study."

The IBS-D Patents' discussion of the RFIB2001 Study is also unavailing. Br. 34-35. As an initial matter, Salix did not raise this argument below. *See* Appx3787 ¶ 183, Appx3744. Furthermore, "there is no presumption, or any reason to assume, that everything disclosed in a patent specification has been invented by the patentee." *Aktiebolaget Karlstads Mekaniska Werkstad v. U.S. ITC*, 705 F.2d 1565, 1574 (Fed. Cir. 1983). Thus, the IBS-D Patents' inclusion of Salix's data from the RFIB2001 study does not establish that the study is the inventors' work.

Finally, Salix's burden-shifting assertion is wrong. Br. 32-33. Norwich presented a *prima facie* case of obviousness based on evidence that the prior art included the RFIB2001 Press Release. Thus, Salix had the "burden of going

forward with rebuttal evidence." *Mahurkar v. C.R. Bard, Inc*., 79 F.3d 1572, 1576-77 (Fed. Cir. 1996). The court found that Salix failed to come forward with such rebuttal evidence at trial, and its arguments on appeal are insufficient.

Unlike this case, the reference in *Google LLC v. IPA Techs. Inc*., 34 F.4th 1081, 1086-87 (Fed. Cir. 2022), identified two named inventors as authors and disclosed elements of the claimed invention. Br. 32-33. The same distinctions apply to Salix's other cited cases. Br. 32-38.

B. The Evidence Supports a Reasonable Expectation of Success Even if the RFIB2001 Press Release Were Not Prior Art.

"The presence or absence of a reasonable expectation of success is [ ] a question of fact." *PAR Pharm., Inc. v. TWI Pharms., Inc*., 773 F.3d 1186, 1196 (Fed. Cir. 2014). Thus, a reasonable expectation of success finding is reviewed for clear error, and "[t]he burden of overcoming the district court's factual findings is, as it should be, a heavy one." *Id*. at 1195 (quotation and citation omitted).

1. The District Court Relied on Other Evidence.

Salix does not argue that the court relied solely on the RFIB2001 Press Release to support any of its obviousness findings. It cannot. The court cited evidence of off-label use, published literature, and two randomized, controlled studies in finding a reasonable expectation of success and rebutting Salix's arguments. Appx36-38. *Contra* Br. 39. It did not commit clear error by considering the RFIB2001 Press Release as "one piece of evidence" in making its

findings . *Vanda Pharms. Inc. v. Teva Pharms. USA, Inc.*, No. 2023-1247, 2023 WL 3335538, at *4 (Fed. Cir. May 10, 2023).

First, the court found that "widespread off-label use reflects a motivation to use rifaximin for the treatment of IBS-D with a reasonable expectation of success." Appx38. *See also* Appx36 (identifying Pimentel's treatment of 900 IBS patients as of 2005 (citing Appx3148-3149, Appx7344-7345)); Appx3366, Appx3370-3371 (Schoenfeld to treat IBS-D patients in 2007); Appx2622-2625 (discussing Appx6894) and Appx3161-3166 (discussing Appx7596 and Appx7588-7589) (Weinstock in 2006-2007); Appx3166-3168 (discussing Appx7261-7266) (Dr. John Jolley in 2006-2007). Real-world evidence that gastroenterologists – who qualify as POSAs – had used the claimed drug to treat the claimed condition is the epitome of a reasonable expectation of success. Appx38. The court cited survey evidence showing that "as of January 2008, 74% of gastroenterologists polled by Salix had prescribed Xifaxan for IBS,"[5] Appx36 (citing Appx7185), and "[p]rescription data show[ing] that 27.7% of Xifaxan 200 mg tablet [213,000] uses in November 2007 had been for IBS," *id*. (citing Appx7144, Appx3353-3354). *See also* Appx3355-3356, Appx7186. This market research "reflects a POSA's state of mind" as of February 2008. Appx39. *See also In re Copaxone Consol. Cases*, 906

[5] "About one third of IBS patients have IBS-D, and there is no evidence in the record that a POSA would expect an IBS-D patient to respond differently to treatment than a patient with another form of IBS." Appx38-39, Appx3143-3144.

F.3d 1013, 1020 (Fed. Cir. 2018) (contemporaneous evidence showing the state of the art).

Second, the "prior art reported success in treating IBS with rifaximin." Appx38. Dr. Pimentel's 2006 book, "*A New IBS Solution, Bacteria – the Missing Link in Treating Irritable Bowel Syndrome*, [ ] recommended the use of rifaxaimin as a safe and effective way to treat IBS-D." Appx37 (citing Appx5868-5870, Appx3144-3145), Appx3366-3368 (discussing Appx5886). Cuoco "disclosed a total dose of 1200 mg for 14 days and reported a significant reduction in the number of patients having IBS symptoms," Appx39 (citing Appx4535), and disclosed that "12 of 23 patients had 'complete resolution of IBS symptoms,'" Appx37 (quoting Appx4538). *See* Appx4536-4537, Appx3179-3182. Barrett disclosed rifaximin "400 mg TID for 1-5 months," Appx39 (citing Appx4799-4800), to eight patients and reported that "rifaximin resulted in complete resolution of clinical symptoms in 4 patients, with no IBS relapse" and that "partial symptom improvement was observed in 4 patients, 3 of whom were treated for an additional 2 months with rifaximin 400 mg three times daily cycle therapy … resulted in a 50% to 70% improvement form baseline," Appx37 (citing Appx4799-4800, Appx3160-3161).

Third, "[r]ifaximin had been shown to be effective in treating IBS in Pimentel 2006 and IBS-D in the RFIB 2001 Protocol, which were randomized, placebo-

controlled clinical trials." Appx38. "Pimentel 2006 taught, 'rifaximin resulted in statistically greater global improvement in IBS than placebo,' and '[i]mprovements were sustained through 10 weeks of follow-up' after 10 days of treatment." Appx37 (citing Appx4644), Appx4639-4641, Appx4643, Appx3169-3172. "The 'RFIB 2001 Protocol' [ ] was a Phase II trial designed to administer rifaximin to patients 18 and over, 550-2,200 mg per day for 14 days for the treatment of IBS-D," and "the protocol included the outcome measures of providing adequate relief of symptoms and evaluating a durability of response over a 12-week post-treatment period." Appx37-38 (citing Appx7047-7055), Appx3173-3177. It published in 2005. Appx3174. "Salix announced the successful completion of this study on September 5, 2007 (the "RFIB 2001 Press Release") and disclosed, 'Top-line results of this study demonstrate that … a 14-day course of rifaximin at 550 mg twice-a-day, provides a statistically significant improvement in both adequate relief of IBS symptoms and adequate relief of bloating, compared to placebo.'" Appx38 (citing Appx7480, Appx3177-3178).

Taken together, the evidence cited by the court is overwhelming, and Salix has not come close to meeting its heavy burden of establishing clear error.

2. Any Error Regarding the RFIB2001 Press Release Is Harmless.

Even if the RFIB2001 Press Release is not prior art, the asserted IBS-D Patent claims would remain obvious. None of the examples cited by Salix show

that the court resolved any issue solely based on the RFIB2001 Press Release. Br. 38. Thus, any error is harmless. *Brown & Williamson Tobacco Corp. v. Philip Morris Inc*., 229 F.3d 1120, 1131 (Fed. Cir. 2000) (finding harmless error).

Salix alleged "flaw[s]" in the prior art and argued that "the RFIB 2001 Protocol did not disclose results…." Appx40-41. The court was "unpersuaded by these arguments," however, finding that "[o]bviousness does not require perfect evidence [ ] and the available evidence persuaded a significant number of doctors who would have been qualified as POSAs to use rifaximin to treat IBS." Appx41. *See also PAR*, 773 F.3d at 1198 ("absolute certainty" not required). Despite Salix's criticisms, the court also found that Pimentel 2006 taught that rifaximin achieved "adequate relief" of IBS symptoms. Appx41.

The court weighed Salix's argument that experts had been skeptical about a link between small intestine bacteria overgrowth ("SIBO") and IBS symptoms, but found that a POSA would not "have discounted prior art sources that were based upon the theory that SIBO contributed to IBS because studies such as the RFIB2001 Protocol were testing that hypothesis at the time." Appx42-43. The SIBO-IBS rationale disclosed in the RFIB2001 Press Release was well known as shown in "prior art sources" cited by the court, and thus could not qualify as the inventors' work. *See, e.g.*, Appx36-37, Appx5074, Appx5096-5097, Appx3138-3141, Appx5868-5870, Appx3144-3145, Appx4536-4538.

The court also rejected Salix's argument concerning antibiotic resistance, crediting testimony of Salix's expert, Dr. Herbert DuPont, that "short-term administration did not raise resistance concerns," Appx43 (citing Appx3014-3015), and Yang's disclosure of a lack of "clinically relevant antibiotic resistance," *id*. (citing Appx7590-7594, Appx3151-3152).

The court gave "some weight to Salix's evidence of skepticism," but concluded that the evidence showed a "small amount of skepticism but not enough to change the outcome of the obviousness analysis." *Id*. *Adapt*, 25 F.4th at 1375 (no clear error where "industry skepticism was not significantly probative of nonobviousness").

Salix has not met its heavy burden of establishing reversible clear error at least because the evidence supporting the court's findings was not limited to the RFIB2001 Press Release.

C. The District Court Correctly Found that the Prior Art Disclosed A Dosage Range that Encompassed the Claimed Dosage Amount.

The court's finding that Pimentel 2006 and the RFIB2001 Protocol disclosed a rifaximin dosage range that encompassed the claimed 1650 mg per day dosage amount is not clearly erroneous, and therefore the court did not commit legal error in applying this Court's overlapping range precedent. Appx39. *Contra* Br. 39-47.

"Where the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine

experimentation." *In re Applied Materials*, 692 F.3d 1289, 1295 (Fed. Cir. 2012) (quotation and citation omitted). *See also E.I. DuPont de Nemours & Co. v. Synvina C.V.*, 904 F.3d 996, 1006 (Fed. Cir. 2018) (finding claims obvious). "A presumption of obviousness applies '[w]here a claimed range overlaps with a range disclosed in the prior art.'" *UCB, Inc. v. Actavis Lab'ys UT, Inc.*, 65 F.4th 679, 689 (Fed. Cir. 2023) (affirming obviousness) (quoting *Ormco Corp. v. Align Tech., Inc.*, 463 F.3d 1299, 1311 (Fed. Cir. 2006)). *See also In re Peterson*, 315 F.3d 1325, 1329 (Fed. Cir. 2003) ("A prima facie case of obviousness typically exists when the ranges of a claimed composition overlap the ranges disclosed in the prior art."). "[A] presumption establishes that, absent a reason to conclude otherwise, a factfinder is justified in concluding that a disclosed range does just that—discloses the entire range." *Almirall, LLC v. Amneal Pharms. LLC*, 28 F.4th 265, 272 (Fed. Cir. 2022) (affirming obviousness).

1. Pimentel 2006 and the RFIB2001 Protocol Disclosed A Dosage Range.

It is well-established that whether a range is disclosed by a single reference or by multiple references is a "distinction without difference." *Iron Grip Barbell Co., v. USA Sports, Inc.*, 392 F.3d 1317, 1322 (Fed. Cir. 2004). The court found that "Pimentel 2006 administered rifaximin, 400 mg TID for 10 days," Appx37 (citing Appx4639-4646), and that the RFIB 2001 Protocol disclosed administering "rifaximin … 550-2,220 mg per day for 14 days for the treatment of IBS-D,"

Appx37-38 (citing Appx7048-7055). Citing the testimony of Norwich's expert, Dr. Albert Harary, the court found that the "RFIB 2001 Protocol taught a range of 1100 to 2200 mg per day for 10-14 days." Appx39 (citing Appx3176-3177 (identifying a dosing range of the RFIB2001 Protocol alone and in combination with Pimentel 2006)). Whether the range disclosed in the RFIB2001 Protocol is considered alone, 550 mg to 2200 mg for 14 days, Appx37, or in combination with Pimentel 2006, Appx3177, the prior art unmistakably disclosed a range that encompassed the claimed dosage amount.

Where "there is a range disclosed in the prior art, and the claimed invention falls within that range, the burden of production falls upon the patentee to come forward with evidence that (1) the prior art taught away from the claimed invention; (2) there were new and unexpected results relative to the prior art; or (3) there are other pertinent secondary considerations." *Galderma Lab'ys, L.P. v. Tolmar, Inc*., 737 F.3d 731, 738 (Fed. Cir. 2013) (reversing trial court and finding claims obvious). Salix contends neither. And, the court found that the evidence of obviousness outweighed Salix's showing of "a small amount of skepticism." Appx44. Thus, Salix failed to meet its burden.

2. Salix's "Positive Result" Mandate Is Unsupported.

Salix attempts to avoid this Court's overlapping-range precedent by inventing a requirement that "positive results" must be shown across the range. Br.

40-41. But none of the cases Salix cites concerns a prior art reference that discloses a range encompassing the claimed dose. Br. 44-45. In *Teva Pharms. USA, Inc. v. Corcept Therapeutics, Inc*., the prior art taught that, when the drug was co-administered, the "dose should be limited to 300 mg per day," which did not encompass co-administering the claimed 600 mg dose. 18 F.4th 1377, 1382-83 (Fed. Cir. 2021). Likewise, in *Endo Pharms. Solutions, Inc. v. Custopharm Inc*., the claim required administering 750 mg of the drug but the lowest dose disclosed in the prior art was 1000 mg. 894 F.3d 1374 (Fed. Cir. 2018). *Ferring B.V*. and *In re Cyclobenzaprine* are inapposite for the same reason. Br. 45.

This Court has expressly rejected the idea that "efficacy data is always required for a reasonable expectation of success." *OSI Pharm., LLC v. Apotex Inc.*, 939 F.3d 1375, 1385 (Fed. Cir. 2019). *See also Acorda Therapeutics, Inc. v. Roxane Lab'ys, Inc*., 903 F.3d 1310, 1334 (Fed. Cir. 2018) ("This court has long rejected a requirement of conclusive proof of efficacy for obviousness.") (quotation and citations omitted). "A finding of a reasonable expectation of success does not require absolute predictability of success." *Almirall*, 28 F.4th at 275 (Fed. Cir. 2022). Here, the court correctly found that, in addition to evidence of "widespread off-label use," "several pieces of prior art reported success in treating IBS with rifaximin," and "[t]he case law does not require 'conclusive

proof of efficacy.'" Appx38 (quoting *Hoffmann-La Roche Inc. v. Apotex Inc*., 748 F.3d 1326, 1331 (Fed. Cir. 2014)). There is no error.

3. The Trial Evidence Supports the Disclosed Range and an Expectation of Success.

Salix distorts the court's analysis. Br. 40-41. The prior art reported that rifaximin was safe and effective in treating IBS-D. Appx39 (citing Appx4640, Appx4535, Appx4799-4800). A POSA would have been motivated to identify an optimal dosing regimen in a placebo-controlled study. Appx39. The RFIB2001 Protocol disclosed a placebo-controlled, dose-ranging study, Appx3174-3175, and a rifaximin dosage range that encompassed the claimed amount. *Id*. *Supra* pp. 47-48.

As the court found, a POSA's reasonable expectation of success in using rifaximin to treat IBS-D was established by "widespread off-label use" and the prior art. Appx38 (off-label use reflects motivation with a reasonable expectation of success), Appx41 ("the available evidence persuaded a significant number of … POSAs to use rifaximin to treat IBS"). Salix's market research and prescription audit data established this motivation and expectation of success. *Supra* pp. 42-43. Appx36 (citing Appx7144, Appx7185, Appx3353-3354), Appx39, Appx7186. The cited prior art supported the same. Appx36 (Pimentel "used rifaximin to treat 900 [IBS] patients" (citing Appx7344-7345, Appx3148-3149), Appx43 (citing Appx7590-7594, Appx3151-3152), Appx37, Appx39 (citing Appx4799-4800).

Norwich presented unrebutted evidence of specific pre-2008 uses of rifaximin in doses above 1200 mg to treat IBS, including IBS-D. For example, in February 2006, Weinstock emailed Forbes about treating an IBS patient, stating that "the real highlight was for me: 90% global [symptom] response with 1800 mg Xifaxan/day x 14 days." Appx6894, Appx2662-2665. Using Weinstock's medical record database, Dr. Harary testified about Weinstock's treatment of specific IBS-D patients with 1800 mg rifaximin (Xifaxan) per day for 14 days. Appx7588-7589, Appx3161-3166, Appx7596 row 14 (1800 mg for 14 days to 72 year old IBS-D patient in August 2006). Likewise, he testified about Jolley's use (in October 2006 thru July 2007) of rifaximin (Xifaxan) 2400 mg per day for 10 days to treat IBS-D patients who had not achieved a desired outcome using 1200 mg per day for 10 days. Appx7261-7266, Appx3166-3168.

Each pre-2008 use in the U.S. by Weinstock and Jolley – corroborated by their articles and medical records – qualifies as prior art under pre-AIA Section 102(a) or (b). Appx3644-3645, Appx3691-3692. When a claimed invention is "used by others in [the United States] before the date of the patentee's invention, the later inventor has not contributed to the store of knowledge, and has no entitlement to a patent." *UCB, Inc. v. Watson Lab'ys Inc*., 927 F.3d 1272, 1289-91 (Fed. Cir. 2019) (patient's invalidating use); *see also Ormco*, 463 F.3d at 1305 (dentist's invalidating use). It was undisputed that physicians can discuss

anonymized uses of rifaximin to treat IBS-D patients, and that patients had no obligation of confidentiality regarding their use of rifaximin. Appx2662-2665, Appx3118-3120, Appx3149, Appx3366. *See Netscape Commc'ns Corp. v. Konrad*, 295 F.3d 1315, 1320 (Fed. Cir. 2002) (a public use is one "by a person other than the inventor who is under no limitation, restriction or obligation of secrecy to the inventor.").

Viscomi 2005, Lin 2006, Lauritano, and Scarpellini – all prior art references found by the court and addressed by Norwich's expert – also support a POSA's reasonable expectation in using rifaximin to treat IBS-D in the claimed dosage amount. Appx33. Viscomi 2005 – appellants' patent application – disclosed "an exemplary dosage range is from 100 to 1800 mg per day" of rifaximin for treating bowel-related disorders, including IBS. Appx4669, Appx4690, Appx4694, Appx3191. *See Boehringer Ingelheim Pharms. Inc. v. Mylan Pharms. Inc*., 803 F. App'x 397, 402 (Fed. Cir. 2020) (claimed 2.5 or 5 mg doses were obvious in view of 1-100 mg range disclosed in a patent publication). Lin 2006 taught administering rifaximin in amounts of about 1200 mg to about 1800 mg for the treatment of chronic fatigue syndrome, and taught that IBS symptoms were present in 92% of such patients. Appx4721, Appx4742, Appx4746-4747, Appx3191-3193.

Lauritano and Scarpellini taught that SIBO is "highly prevalent in patients with IBS," and that increasing doses of rifaximin achieved superior efficacy in reducing SIBO. Appx7267-7271, Appx4663-4667, Appx3185-3188. Finding a motivation "to combine the prior art to achieve a dosage regimen within the known range," the court credited Pimentel 2006's teaching – based on a citation to Lauritano – that "the optimal dosage may, in fact, be higher than that used in our study." Appx39 (citing Appx4644), Appx3183-3184, Appx3188-3189. Moreover, Scarpellini, published after Pimentel 2006, taught that administering rifaximin 1600 mg per day to patients, including IBS-D patients, achieved greater efficacy than giving 1200 mg without differences in side effects. Appx4663-4664, Appx4666-4667, Appx3186-3189. "A recognition in the prior art that a property is affected by the variable is sufficient to find the variable result-effective." *Applied Materials*, 692 F.3d at 1297. *See also* Appx114 (identifying "effective dosage levels … using routine pharmacological methods").

Thus, the evidence showed that physicians knew how to safely and effectively dose rifaximin within the "workable range" disclosed by Pimentel 2006 and the RFIB2001 Protocol with a reasonable expectation of success. The court drew reasonable inferences from the pervasive off-label use by POSAs before 2008, the prior art, and the known safety profile of rifaximin. *See Acorda*, 903 F.3d at 1334 (a POSA "can draw reasonable inferences about the likelihood of

success even without a perfectly designed clinical trial"). The court agreed with Norwich's view of the evidence. It was not required "to credit the unsupported assertions of [Dr. Schoenfeld]" concerning the RFIB2001 Protocol. Br. 43; *Rohm & Haas Co. v. Brotech Corp*., 127 F.3d 1089, 1092 (Fed. Cir. 1997). Regardless, it was "unpersuaded" by Salix's arguments. Appx41-42. "Determining the weight and credibility of the evidence is the special province of the trier of fact." *Inwood Lab'ys, Inc. v. Ives Lab'ys, Inc*., 102 S.Ct. 2182, 2189–90 (1982). Salix can point to no clear error.[6]

D. The Proposed Amici Address New or Nonexistent Issues.

Whether there is a reasonable expectation of success is case-specific. *Acorda*, 903 F.3d at 1333. Here, the court did not solely rely on the RFIB2001 Protocol in finding a reasonable expectation of success, and the record contrasts starkly to the utter absence of data in *OSI*. *Supra* pp. 41-44, 50, Appx42. *Contra* ECF No. 31-2 ("Regeneron Br.") 6-8, ECF No. 35-2 "Vanda Br." 12-13. There is no *per se* rule that this reference cannot be considered or contribute to a finding of a reasonable expectation of success. *Vanda*., 2023 WL 3335538, at *4. Nor should this Court apply a special rule that presumes failure based on irrelevant clinical studies. Regeneron Br. 6-7, Vanda Br. 12.

[6] This Court should decline to render judgment in the first instance on prior art combinations that the court did not reach below. Br. 48. *See Baxter Healthcare Corp. v. Spectramed, Inc*., 49 F.3d 1575, 1585 (Fed. Cir. 1995).

Courts "do not generally entertain arguments [from a proposed *amicus*] that were not raised below and are not advanced … by any party." *Burwell v. Hobby Lobby Stores, Inc.*, 134 S. Ct. 2751, 2776 (2014). It is undisputed that the RFIB2001 Protocol qualifies as prior art under pre-AIA Section 102(b). *Contra* Vanda Br. 4, 9-27 (disputing prior art status and raising experimental use doctrine). Nor did Salix make any argument below about any "mandated" disclosure of the RFIB2001 Protocol. Br. 42. In any event, the cited regulation, 42 C.F.R. § 11.22, did not apply because RFIB2001 was initiated and completed before September 27, 2007. Vanda Br. 5-6.

Clinical trial disclosures do not pose dire patentability consequences. Regeneron Br. 11-14, Vanda Br. 9-10. They do not dictate a conclusion of obviousness, as shown by Salix's and its amici's cases. *See* Br. 42 (citing *Sanofi-Aventis U.S. LLC v. Sandoz*, Inc., No. 20-804, 2023 WL 4175334, at *14 (D. Del. June 26, 2023) (finding ongoing trial for prostate cancer insufficient where prior art showed efficacy in breast cancer), Regeneron Br. 14, Vanda Br. 12-13. Prophetic examples may provide support for a claimed invention, and, in fact, Salix relied on prophetic examples here. Appx45 (finding "proposed study" sufficient). Regardless, "[s]cientific confirmation of what was already believed to be true may be a valuable contribution, but it does not give rise to a patentable

invention." *PharmaStem Therapeutics, Inc. v. ViaCell, Inc.*, 491 F.3d 1342, 1363-64 (Fed. Cir. 2007) (citations omitted).

V. THE DISTRICT COURT CORRECTLY HELD THAT THE POLYMORPH PATENTS ARE INVALID.

The court's obviousness determination is well-supported by the facts established at trial. It is undisputed that "Cannata disclosed crystalline rifaximin" having "strong antibacterial properties and low bioavailability" that would have motivated a POSA to consider it as a potential drug candidate.[7] Appx6, Appx12-13, Appx16, Appx4528-4531, Appx4901-4902, Appx3383-3384, Appx3390-3391, Appx3412-3413. The court found that "regulatory bodies instructed applicants to characterize the solubility, stability, and bioavailability of drug candidates," especially if the candidate was a hydrate.[8] Appx7, Appx13 (citing Appx7014, Appx7018, Appx3413-3416). It also recognized that "no rifaximin had been publicly characterized as a particular form as of the priority date" and that a POSA would have known "about the potential for a hydrate to form, and be motivated to perform routine testing … for water content and hydrate formation" because

[7] Salix admits that a crystalline compound is necessary for polymorphism. Br. 20-22. *See also* Appx3409, Appx3417-3418.

[8] "A hydrate is a class of crystal form in which water is inside the crystal lattice." Appx3396. As Dr. Zaworotko explained, a POSA would have known that water content may affect a hydrate's structure and, correspondingly, its solid-state stability and XRPD profile. Appx3417-3420, Appx4467, Appx4476. A POSA would have been motivated to use the most stable form of the compound in a drug product. Appx3415, Appx3421. *See also* Appx3421-3422, Appx3427.

Cannata teaches ethanol and water as a solvent to prepare rifaximin. Appx13 (citing Appx7046, Appx4656, Appx7018, Appx3409-3411), Appx4529-4531, Appx3384-3385, Appx3392-3393, Appx3417-3420. The court also found that crystalline materials are identified by their XRPD peaks. Appx6, Appx13 (citing Appx7017, Appx3415-3416), Appx3480; Br. 20. Salix does not dispute these factual findings. Accordingly, the court correctly found that "a POSA would have been motivated to characterize the rifaximin produced by the Cannata processes." Appx13.

The court also properly found that "a POSA would have a reasonable expectation of success in characterizing the polymorph β, as opposed to the other forms of rifaximin." Appx14-15, Appx7. The Viscomi Declaration (Appx4845-4856) discloses that "rifaximin prepared according to Cannata yielded β along with other polymorphs." Appx14, Appx4846, Appx3400-3401, Appx3450, Appx3489-3492. The court credited Dr. Zaworotko's testimony that "[B]eta is the winner in terms of stability under normal conditions of temperature and humidity." Appx14, Appx3398-3399, Appx3426-3427. It also found that water content and x-ray powder diffraction ("XRPD") peaks are "'inherent' properties of a crystal form that can be tested using routine methods." Appx15, Appx6, Appx3392-3393, Appx3404-3407, Appx3415-3416. Therefore, the court found that a POSA would have a reasonable expectation in identifying rifaximin β having the claimed water

content and XRPD peaks because it "is a commonly produced polymorph and the most stable form of rifaximin." Appx14.

Salix has not met the heavy burden of establishing that the court's findings are clearly erroneous, and this Court should affirm. Alternatively, this Court should affirm invalidity of the Polymorph Patents because Cannata inherently anticipates rifaximin β.

A. The District Court Applied the Correct Motivation for the POSA to Combine the Prior Art.

The crux of Salix's argument on appeal is that the court applied the wrong motivation inquiry. Br. 48-51, 55-57. Citing *Pharmacyclics* and *Grunenthal,* Salix contends that "challengers to polymorph claims" must prove that the POSA "had a motivation [to] develop[] the specific claimed polymorph." *Id.* at 51. Salix is wrong.

1. Obviousness Does Not Require that a POSA's Motivation to Combine the Prior Art Be the Same as the Inventor's.

As an initial matter, the court did not apply "the wrong test" for obviousness. Br. 55. *Pharmacyclics* does not set forth a specialized "polymorph obviousness analysis," and there is no special test "to evaluate whether … a specific polymorph is obvious." Br. 49, 55. Rather, *Graham* and *KSR* govern the obviousness inquiry here as in any other case. *See generally*, *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398 (2007); *Graham v. John Deere Co. of Kansas City*, 383 U.S. 1 (1966).

Furthermore, a POSA's motivation to combine the prior art is "not limited to the same motivation that may have motivated the inventors." *PAR*, 773 F.3d at 1197. On the contrary, the "[m]otivation to combine may be found in many different places and forms." *Allergan, Inc. v. Sandoz Inc.*, 726 F.3d 1286, 1292 (Fed. Cir. 2013). In *PAR*, for example, this Court rejected a patentee's contention that the POSA's motivation to combine had to be the claimed food effect, even though "the food effect was not known in the art at the time of the invention." *PAR*, 773 F.3d at 1197. Similarly, here, no *specific* crystal form of rifaximin had been characterized in the prior art and a POSA thus could not have been motivated by rifaximin β specifically to combine the prior art. This Court did not hold otherwise in *Pharmacyclics*, but held only that the lower court had not clearly erred in its motivational finding *on the facts of that case*. *Pharmacyclics LLC v. Alvogen, Inc.*, No. 2021-2270, 2022 WL 16943006, at *10-11 (Fed. Cir. Nov. 15, 2022).[9] Indeed, if Salix's contention about motivation were correct, no uncharacterized or unknown crystal form (or compound, for that matter) could ever be obvious.

[9] The unpublished *Bristol-Myers* decision (Br. 51, 57) had a very different factual record than is present here and predates *KSR* and its abrogation of the "teaching, suggestion, motivation" test.

2. The Court Applied the Correct Motivation to the POSA.

"The determination of obviousness is dependent on the facts of each case." *Sanofi-Synthelabo v. Apotex, Inc.*, 550 F.3d 1075, 1089 (Fed. Cir. 2008); *Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348, 1366 (Fed. Cir. 2007). Thus, and as Salix recognized, this Court affirmed both *Pharmacyclics* and *Grunenthal* based on the district courts' factual findings specific to those cases. Br. 50-51 (citing *Pharmacyclics*, 2022 WL 16943006, at *10-11; *Grunenthal GMBH v. Alkem Lab'ys Ltd.*, 919 F.3d 1333, 1343-44 (Fed. Cir. 2019)).

The facts of this case compelled the court to find a different motivation than the courts in *Pharmacyclics* and *Grunenthal*. In *Pharmacyclics*, the prior art only disclosed that ibrutinib "'*may* be in various forms,' including crystalline forms." *Pharmacyclics*, 2022 WL 16943006, at *5-6 (emphasis added). There were no teachings "that any crystalline forms of ibrutinib actually exist" and "none of the references disclosed such a crystalline form." *Id.* Nor did the references provide any particular guidance about how to produce a crystalline form. *Pharmacyclics LLC v. Alvogen Pine Brook LLC*, 556 F. Supp. 3d 377, 411 (D. Del. 2021). In *Grunenthal*, the prior art disclosed a different crystalline form than the claimed form and it was unknown whether other crystalline forms existed. *Grunenthal*, 919 F.3d at 1337, 1341. Furthermore, the prior art "provided insufficient guidance" about how to produce the claimed form. *Id.* at 1341-43.

In contrast to the facts of *Pharmacyclics* and *Grunenthal*, the court here correctly found that "Cannata disclosed crystalline rifaximin, methods of making it, and that it had antibacterial properties." Appx6. Thus, unlike in those cases, a POSA would not have to search for a *new* crystalline form – the prior art already disclosed one. The court also correctly found that, unlike in *Grunenthal*, the disclosed crystalline form of rifaximin had not been "publicly characterized" or evaluated for polymorphism. Appx13. Therefore, characterizing Cannata's crystalline rifaximin (e.g., its stability, water content and XRPD profile) would have been the logical next step for a POSA in view of FDA's guidance (Appx6980-7027), especially knowing that the crystalline rifaximin had been obtained from water. *See* Appx7, Appx13, Appx3412-3422. *See also Allergan*, 726 F.3d at 1291-92 (recognizing FDA approval as relevant and properly considered in evaluating motivation). Based on these facts, which differ materially from the facts in *Pharmacyclics* and *Grunenthal*, the court correctly found that "[a] POSA would have had a motivation to combine Cannata with commonly known testing techniques [for crystal form and water content] because regulatory bodies instructed applicants to characterize the solubility, stability, and bioavailability of drug candidates." Appx7.

There is no legal basis for blindly demanding the same motivation to combine the prior art in all polymorph cases, as Salix suggests. Br. 49-51, 55-57.

On the contrary, doing so would defy the "expansive and flexible approach" required by the Supreme Court. *KSR*, 550 U.S., at 415. Here, the court correctly framed the obviousness inquiry "based on its understanding of the problem facing [POSAs] at the time the invention was made." *Insite Vision Inc. v. Sandoz, Inc.*, 783 F.3d 853, 859 (Fed. Cir. 2015). Salix does not dispute the facts the court relied on (Appx12-13) to define the POSA's motivation. "The burden of overcoming the district court's factual findings is, as it should be, a heavy one," which Salix has failed to carry.[10] *Polaroid Corp. v. Eastman Kodak Co.*, 789 F.2d 1556, 1559 (Fed. Cir. 1986). Accordingly, Salix has failed to show any clear error that justifies displacing the court's finding.

B. The District Court Correctly Found That a POSA Would Have a Reasonable Expectation of Successfully Characterizing Cannata's Crystalline Rifaximin.

The court correctly found that "[a] POSA would have had a reasonable expectation of success at characterizing the rifaximin β polymorph and arriving at the claimed XRPD peaks … and water content." Appx7. Although the court erred in not finding that rifaximin β is the natural result of Cannata's teaching (*see infra* Section V.C), it correctly found that "polymorph β is a commonly produced polymorph and the most stable form of rifaximin." Appx14. Moreover, it properly

[10] Unlike the patentees in *Pharmacyclics*, 556 F. Supp. 3d at 412-413, Salix also did not offer any "evidence of secondary considerations of nonobviousness for the Polymorph Patents" (Appx15).

found that water content and XRPD peaks are "inherent characteristics" of a crystalline form and "can be tested using routine methods." Appx6, Appx15, Appx3392-3393, Appx3404-3407, Appx3415-3416.

Echoing its legally incorrect assertion about motivation, Salix contends that a POSA "would not have been able to predict in advance [rifaximin β's] existence" and its properties and could not "have a reasonable expectation of success to find something you don't know exists." Br. 52-53 (quoting Appx3459), 55-57 (quoting Appx3478). The court correctly rejected this argument, explaining that "the expectation of success need only be reasonable, not absolute." Appx14 (quoting *Pfizer*, 480 F.3d at 1364). If knowledge of that which is claimed were required for a reasonable expectation of success, no new form (or salt, or compound, etc.) would be obvious. On the contrary, this Court has made clear "that [a reasonable expectation] does not require a *certainty* of success." *Medichem*, 437 F.3d at 1165.[11] And obviousness may be found even where there is "some degree of unpredictability in the art." *Pfizer*, 480 F.3d at 1364. *See also Allergan*, 726 F.3d at 1292-93; *In re O'Farrell*, 853 F.2d 894, 903-04 (Fed. Cir. 1988).

[11] It is irrelevant that neither *Pfizer* nor *Medichem* "is a polymorph case" (Br. 57) because they reaffirm a basic principle of patent law. *Pfizer*, 480 F.3d at 1364; *Medichem*, 437 F.3d at 1165. Indeed, this Court cited both decisions in *Grunenthal*. *Grunenthal*, 919 F.3d at 1342-44.

Salix's arguments also ignore the scientific facts of this case. As discussed, Cannata disclosed crystalline rifaximin that had not yet been publicly characterized and the use of a crystallization solvent comprising water, which a POSA would have recognized could lead to formation of a hydrate. *Supra* pp. 56-57, 61. Therefore, rather than performing a full, "trial-and-error" polymorph screen as Salix suggests (Br. 21, 53), a POSA would have simply characterized the crystalline rifaximin obtained in Cannata by "routine testing" of its XRPD peaks and water content. Appx13. Salix does not dispute these facts.

Nor does Salix dispute the natural relationship between the water content of rifaximin and its crystalline form. The uncontroverted trial record is that rifaximin β converts to rifaximin α, δ, and ε when it loses water (i.e., is dehydrated, such as by drying) and then reforms when rifaximin α, δ, and ε gain water (i.e., is hydrated, such as by exposure to humidity). *See, e.g.*, Appx4702, Appx4704-4705, Appx3397-3399. In other words, all roads lead through rifaximin β during synthesis of rifaximin α, δ, and ε,[12] as the named inventors clearly depicted in the figure below:

[12] Rifaximin β "is prepared from wet rifaximin." Appx3397, Appx4700, Appx4702, Appx4705, Appx5007.

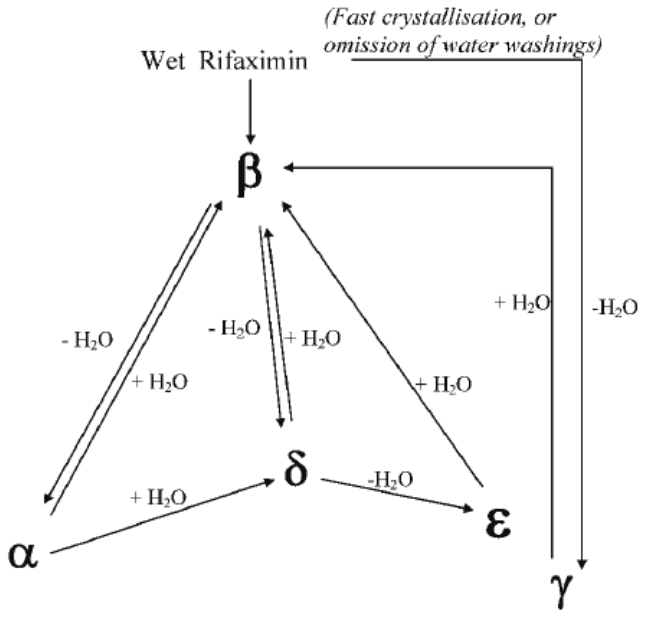

Fig. 4 The relationship between the various crystal forms of rifaximin.

Appx4705. The inventors further explained that rifaximin β has a water content of 6% to 40% and that "drying wet rifaximin, or the rifaximin β form" to lower water contents produces rifaximin α (at less than 3% water), rifaximin δ (at 4% - 6% water), and rifaximin ε (by further drying rifaximin δ). Appx4700, Appx4702, Appx4705, Appx5007, Appx3396-3398, Appx3444-3448.

Cannata's process does not disclose drying crystalline rifaximin during synthesis and thus its water content would have been greater than 6%. Appx3391-3393, Appx3396-3398, Appx3407-3409. Therefore, rifaximin β is inevitably produced by following the Cannata processes because the as-synthesized rifaximin has an initial water content above the levels of rifaximin α, δ, and ε. *Id*. *See also* Appx4700, Appx4702, Appx4705, Appx5007, Appx3446-3448. Thus, even if rifaximin α, δ, or ε was formed by drying the resulting rifaximin to less than 5%

water content, rifaximin β would have necessarily formed as an intermediate during synthesis. Appx4700, Appx4702, Appx4705, Appx3401-3402, Appx3442-3443. Moreover, rifaximin α, δ, and ε each revert to rifaximin β under ambient temperature and humidity. Appx4702, Appx4704-4705, Appx3398-3399, Appx4847, Appx3401. As Dr. Zaworotko explained – and the court credited – "[B]eta is the winner in terms of stability under normal conditions of temperature and humidity." Appx14, Appx3398-3399, Appx3421-3422, Appx3426-3427. Thus, rifaximin β is the natural result of Cannata's process. *Infra* Section V.C.

Finally, the court did not "erroneously conflate[] actual success and the expectation of success." Br. 49. Instead, the court credited the evidence showing that Cannata's process at the very least "commonly produce[s]" polymorph β, the most stable form of rifaximin.[13] Appx14. *See, e.g., Hospira, Inc. v. Fresenius Kabi USA, LLC,* 946 F.3d 1322, 1329-30 (Fed. Cir. 2020) (evidence published after the priority date "can be used to demonstrate what is 'necessarily present' in a prior art embodiment"). The court found that the Viscomi Declaration admits that "[r]ifaximin prepared according to the old patent[]" Cannata yielded rifaximin β, α,

[13] "[Salix] has cited no authority, and there can be none, to support its suggestion that [this Court] substitute an independent, de novo evaluation of [Dr. Myerson's] testimony for that made by the district court." *Polaroid*, 789 F.2d at 1573. Indeed, where there are multiple "permissible views of the evidence, the fact-finder's choice between them cannot be clearly erroneous." *Genentech, Inc. v. Sandoz Inc.*, 55 F.4th 1368, 1376 (Fed. Cir. 2022) (quoting *Hospira*, 946 F.3d at 1328).

δ, or ε, and mixtures thereof. Appx4846, Appx14, Appx3400-3401, Appx3450, Appx3489-3492. Although post-dated art, the named inventor's declaration thus "helps to elucidate what [Cannata's rifaximin] consisted of" – i.e., rifaximin β and/or polymorphs with lower water contents to which rifaximin β was a necessary precursor during synthesis.[14] *Hospira*, 946 F.3d at 1330. *See also Monsanto Tech. LLC v. E.I. DuPont de Nemours & Co.*, 878 F.3d 1336, 1345 (Fed. Cir. 2018) (finding that inventor declarations "do not expand the meaning of [a reference] or serve as prior art: they demonstrate what is inherent" in the prior art). Although not every batch produced rifaximin β alone, production of polymorphs to which it was a necessary precursor is sufficient to show obviousness. *See SmithKline Beecham Corp. v. Apotex Corp.*, 403 F.3d 1331, 1344-45 (Fed. Cir. 2005) (finding patent invalid because a prior art process produced "at least trace amounts" of the claimed compound); *Hospira*, 946 F.3d at 1332 ("If a property of a composition is in fact inherent, there is no question of a reasonable expectation of success in achieving it.").

[14] Similarly, Viscomi 2008 (Appx4700-4707) and Braga 2012 (Appx5007-5014), which also were authored by named inventors, explain the inherent properties of and relationship between the rifaximin β, α, δ, and ε crystalline forms produced by Cannata's process. Appx4700, Appx4702, Appx4704-4705, Appx5007, Appx3393-3402. Therefore, these articles also elucidate what is necessarily present in Cannata's disclosures.

"The presence or absence of a reasonable expectation of success is … a question of fact." *PAR*, 773 F.3d at 1196. *See also Medichem*, 437 F.3d at 1165. Salix has not shown that the court's determination of reasonable expectation of success is clearly erroneous, and this Court should thus affirm the obviousness finding.

C. Alternatively, Claim 4 of the '199 Patent Is Invalid As Inherently Anticipated.

If this Court determines that claim 4 of the '199 patent is not invalid as obvious, it should affirm the invalidity ruling on the alternative ground that claim 4 is inherently anticipated by Cannata.

As discussed above, the Viscomi Declaration demonstrates that Cannata produces rifaximin β, α, δ, or ε, and mixtures thereof. *Supra* pp. 57, 66-67. The natural relationship between these forms is undisputed. *Supra* pp. 64-66. Moreover, it is an inherent property of rifaximin that form β exists at water contents above 5%, whereas rifaximin α, δ, and ε exist at water contents below 5%. *Supra* p. 65. Furthermore, Cannata necessarily produces rifaximin β (having a water content of 6% to 40%) because no drying step is disclosed, and drying rifaximin β results in rifaximin α, δ, and ε. *Supra* pp. 65-66. Thus, Cannata necessarily produces rifaximin β either directly or as an intermediate during the synthesis of rifaximin α, δ, or ε. *Supra* pp. 65-66. Salix offered no evidence to the contrary, or dispute that the water content and XRPD profile are inherent

characteristics of rifaximin β. *Supra* pp. 57, 62-63. The evidence therefore proves that practicing Cannata's method "naturally results" in rifaximin β.[15] *SmithKline*, 403 F.3d at 1343-44. *See also Atlas Powder*, 190 F.3d at 1347-49.

The court's failure to find inherency based on this evidence was clearly erroneous. The court first found that "[t]he Viscomi Declaration does not help Norwich" because it shows that four batches prepared according to Cannata did not contain rifaximin β but rather one or a mixture of rifaximin α, δ, or ε. Appx10. This finding misses the point, however, which is that the Viscomi Declaration shows that practicing Cannata provides *only* rifaximin β, α, δ, and ε, and that the latter three – rifaximin α, δ and ε – *cannot* form without first going through rifaximin β.[16] The declaration thus demonstrates inherency.

[15] This Court has also "reject[ed] the contention that inherent anticipation requires recognition in the prior art." *Schering Corp. v. Geneva Pharms., Inc.*, 339 F.3d 1373, 1377-78 (Fed. Cir. 2003). "Insufficient prior understanding of the inherent properties of a known composition does not defeat a finding of anticipation." *Atlas Powder*, 190 F.3d at 1349. *See also SmithKline*, 403 F.3d at 1345 (finding a polymorph that is the "natural derivative" of practicing the prior art inherently anticipated).

[16] The court improperly found that Viscomi 2008 does not demonstrate that "rifaximin α, δ, and ε are necessarily derived from rifaximin β" because the relationship between rifaximin's crystalline forms was "not the main point of the article." Appx9-10. On the contrary, the article reports on studies "identify[ing] crystal forms of rifaximin" and their properties, including "investigat[ing] the transformation of one form of rifaximin to another." Appx4700, Appx4702, Appx4705.

The court next pointed out that "Viscomi 2008 discloses steps that are more specific than what Cannata describes." Appx10-11. These differences are inconsequential. As a preliminary matter, the asserted claims are product claims, making the process irrelevant. *See, e.g.*, *Amgen Inc. v. F. Hoffman-La Roche Ltd.*, 580 F.3d 1340, 1366 (2009) ("[A]n old product is not patentable even if it is made by a new process."). But the key point is that Viscomi 2008 and Cannata prepared "wet rifaximin." Appx10-11, Appx4700, Appx4529-4531, Appx3391-3392, Appx3395-3398. "Wet rifaximin" necessarily has a water content exceeding 6%, which undisputedly is the condition that necessarily produces rifaximin β. *Supra* pp. 64-66. The added "precision" in the steps in Viscomi thus only further demonstrates inherency.

The court's discussion of Bacchi 2008 (Appx6671-6682) is similarly erroneous. Appx11. While Bacchi used a "slow evaporation" step, the relevant fact is that Bacchi also inevitably produced wet rifaximin that led to rifaximin β inherently having the same water content and XRPD profile. *See* Appx6674, Appx6678, Appx6681, Appx5007, Appx5009, Appx3402-3404, Appx3474.

Finally, the court incorrectly held that Norwich failed "to show that, no matter how the chemist exercised his or her discretion [in following Cannata], rifaximin β would be produced." Appx11. Both the Viscomi Declaration (practicing Cannata) and Viscomi 2008 discuss the same rifaximin polymorphs:

rifaximin β, α, δ, and ε. Rifaximin γ, the only other polymorph discussed in Viscomi 2008, is produced by fast crystallization. *See* Appx4705. But Salix's expert, Dr. Myerson, testified that Cannata discloses a 7:3 ethanol-water solution for the crystallization solvent, which "eliminates the possibility of" using fast evaporation (Appx3474) and thus production of rifaximin γ. Moreover, there is no dispute that there is a natural relationship between the water content of rifaximin and its crystalline forms such that rifaximin β necessarily forms at 6% or higher water content, a level necessarily present in "wet rifaximin."[17] Norwich therefore proved by clear and convincing evidence that Cannata invariably produces rifaximin β. *PAR*, 773 F.3d at 1195 (stating that inherency applies "when the limitation … is the 'natural result' of the combination of prior art elements."). Finally, Salix offered no evidence that process differences make any *actual* difference in the variety of polymorphs produced. This Court should thus affirm the district court's invalidity ruling based on the alternative ground of anticipation over Cannata.

[17] For the same reason, the case law stating that "[e]xperiments that do not follow the prior art procedure alleged to inherently anticipate cannot show inherent anticipation" is inapposite. Appx11. The Viscomi Declaration experiments *did* follow Cannata and the supporting references likewise prepared wet rifaximin, which is what matters.

D. Salix Has Not Identified Any Independent Basis For Clear Error Pertaining Only to Claim 36 of the '206 Patent.

Claim 36 of the '206 patent recites "[a] solid pharmaceutical composition comprising" rifaximin β and a "pharmaceutically acceptable excipient or carrier." Appx100. Salix has not identified any clear error pertaining to the "pharmaceutically acceptable excipient or carrier" and failed to rebut Norwich's arguments at trial. Appx15-16. Because rifaximin β was properly found obvious or anticipated for the reasons discussed herein, the court should affirm the court's judgment as to claim 36 of the '206 patent.

CONCLUSION

For the reasons set out above, this Court should revise the Final Judgment as Norwich requested and affirm the District Court's judgment that the IBS-D and Polymorph Patents are invalid as obvious, or, alternatively, reverse or vacate the District Court's judgment that claim 4 of the '199 patent is not invalid as inherently anticipated.

Dated: August 22, 2023

Respectfully submitted,

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FORM 19. Certificate of Compliance with Type-Volume Limitations **Form 19**
July 2020

UNITED STATES COURT OF APPEALS
FOR THE FEDERAL CIRCUIT

CERTIFICATE OF COMPLIANCE WITH TYPE-VOLUME LIMITATIONS

Case Number: 22-2153, 23-1952

Short Case Caption: Salix Pharmaceuticals, Ltd. v. Norwich Pharmaceuticals Inc.

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